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ORIGINAL ARTICLES

STUDIES IN MYASTHENIA GRAVIS—A RAPID DIAGNOSTIC TEST 153
K. E. Osserman, M.D., and Paul Teng, M.D., New York

TREATMENT OF MYASTHENIA GRAVIS WITH MESTINON BROMIDE 156
J. E. Tether, M.D., Indianapolis

THE ANTERIOR APPROACH TO THE STELLATE GANGLION 158
D. C. Moore, M.D., and L. D. Bridenbaugh Jr., M.D., Seattle

USE OF BENZATHINE PENICILLIN G IN CARRIERS OF GROUP A BETA-HEMOLYTIC STREPTOCOCCI 162
Lieut. T. J. Brooks Jr. (MC), U. S. N. R., and Capt. T. I. Moe (MC), U. S. N.

PORPHYRIA AND PREGNANCY 165
J. B. Durst, M.D., and M. A. Krembs, M.D., Milwaukee

LEVALLORPHAN (LORFAN) AND ALPHAPRODINE (NISENTIL) IN ANESTHESIA 168
F. F. Foldes, M.D.; Elia Lipschitz, M.D., G. M. Weber, M.D., Pittsburgh; Mark Swerdlow, M.D., F.F.A.R.C.S., Manchester, England, and L. A. Pirk, Ph.D., Nutley, N. J.

CONTROLLED ANALGESIA WITH CONTINUOUS DRIP MEPERIDINE 175
H. M. Ausherman, M.D., Charlotte, N. C.; W. K. Nowill, M.D., Elmira, N. Y., and C. R. Stephen, M.D., Durham, N. C.

USE OF CHLORPROMAZINE AND RESERPINE IN THE TREATMENT OF EMOTIONAL DISORDERS 179
W. W. Zeller, M.D.; P. N. Graffagnino, M.D.; C. F. Cullen, M.D., and H. J. Rietman, M.D., Hartford, Conn.

EXPERIMENTAL INVESTIGATIONS ON MECHANISM PRODUCING ACUTE DERMATOPHYTOSIS OF FEET 184
R. L. Baer, M.D.; S. A. Rosenthal, Ph.D., New York; J. Z. Litt, M.D., Cleveland; and Hymen Rogachefsky, M.D., Rochester, N. Y.

THE BIOPHYSICAL BASIS OF PHYSICAL MEDICINE 191
H. P. Schwan, Ph.D., Philadelphia

CLINICAL ASPECTS OF HYPERINSULINISM 198
H. D. Breidahl, M.D.; J. T. Priestley, M.D., and E. H. Rynearson, M.D., Rochester, Minn.

CLINICAL NOTES

RENAL LESIONS OF SULFONAMIDE TYPE AFTER TREATMENT WITH ACETAZOLAMIDE (DIAMOX) 204
A. S. Glushien, M.D., and E. R. Fisher, M.D., Pittsburgh

THROMBOCYTOPENIA FOLLOWING ACETAZOLAMIDE (DIAMOX) THERAPY 206
E. H. Reisner Jr., M.D., and M. C. Morgan, M.D., New York

NEW MUSCLE FORCEPS FOR PTOSIS OPERATIONS AND SURGERY OF THE SUPERIOR OBLIQUE 207
Conrad Berens, M.D., New York

SPECIAL REPORTS

Council on Pharmacy and Chemistry

CURRENT STATUS OF THERAPY IN NAUSEA AND VOMITING OF PREGNANCY 208

EDITORIALS

Commonwealth Fund and Ford Foundation Support Medical Education 210
Urinary Infections 210
Dermatophytosis of the Feet 211

REGULAR DEPARTMENTS

Council on Medical Education and Hospitals: Supplementary List—Corrections 212
Bureau of Medical Economic Research: Illnesses Treated by Physicians 213
F. G. Dickinson, Ph.D.
Medical News 215
Correction 220
Meetings 220
Examinations and Licensure 222
Magazine-Television Report 222
Deaths 223
Foreign Letters:
Brazil: Extrahepatic Biliary Lesions. Epidemic Typhus. Pyloric Stenosis. Postoperative Care 225
England: Control of Hospital Cross Infection. Munchausen Syndrome. Fellowship for Freedom in Medicine. Prednisone and Prednisolone. A New Antibiotic. Somatotypes in Diabetes. Cuts in National Health Service. Domiciliary Consultations by Specialists. Chinese Eggs and Food Poisoning. Rockefeller Grants. Mitral Valvotomy. Mental Health Exhibit. College of Physicians and Surgeons of South Africa. Queen Visits Veterinary School. After-Care of Patients. Chemical Microbiology 225
Germany: Health Insurance 228
Italy: Poliomyelitis in Italy 228
New Zealand: Primary Aldosteronism. Effects of Halocortisols and Prednisone on Cutaneous Homotransplants. Chemically Induced Granulomas. Hypothermia in Sheep 229
Switzerland: Prolonged Treatment with Cortisone 229
Correspondence:
Emphysema. Poliomyelitis Vaccine. Drug Samples 230
Business Practice:
Physical Factors in Building a Medical Unit 233
Medical Literature Abstracts 237
Book Reviews 247
Queries and Minor Notes:
Keloids Following Thyroidectomy. Exposure to Trichloroethylene. Waterpipe Smoking and Lung Cancer. Bactericide for Swimming Pool. High Blood Sugar Level. Aspermia During Intercourse. Keratoconus. Hysterectomy. Osteitis Deformans. Canned Food. Use of Stethoscope by Physical Educators. Nasal Polyps. High Leucocyte Count in Asymptomatic Man 248

WASHINGTON NEWS

Health Bills. Mental Illness Support. Medical Subsidies. Tests and Studies. Narcotics. Communicable Diseases. Pan American Health Problems. ..... Adv. Page 13
State Medical Associations ..... Adv. Page 16
Tonics and Sedatives ..... Adv. Page 58
The Bright Side ..... Adv. Page 80
Books Received ..... Adv. Page 82
Index to Advertisers ..... Adv. Page 90

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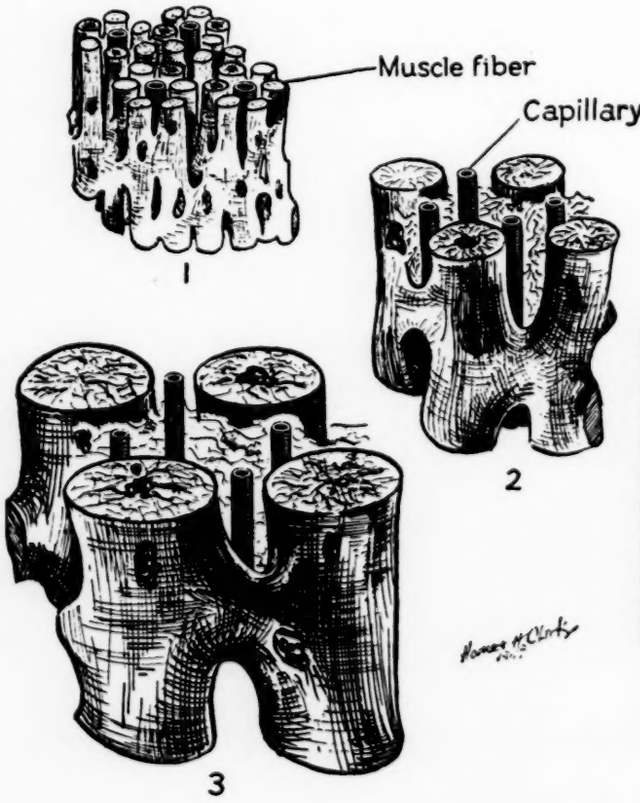

Sketch showing the vascular changes in heart muscle attending growth and hypertrophy. 1, From the heart of a newly born with normal concentration of capillaries, each supplying about six small fibers. 2, From a normal adult heart with the same concentration of capillaries in the ratio of one fiber for each capillary. 3, From a hypertrophied heart with a low concentration of capillaries which have not multiplied with increased size of fibers.

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STUDIES IN MYASTHENIA GRAVIS—A RAPID DIAGNOSTIC TEST

FURTHER PROGRESS WITH EDROPHONIUM (TENSILON) CHLORIDE

Kermit E. Osserman, M.D.
and
Paul Teng, M.D., New York

• Edrophonium chloride is a cholinergic drug characterized by prompt, brief action on patients with myasthenia gravis. The response consists of temporary increase in muscle strength and general subjective improvement. If the diagnosis has been correct there is no ensuing fasciculation in the muscles and side-effects are minimal. If the subject is psychoneurotic with abnormal fatigability, the effects of the drug can be duplicated by giving a placebo. If the subject is normal, there is usually fasciculation without increase in strength. Excessive doses of the drug elicit false-positive reactions in a small group of hyperreactive subjects. The recommended dosage, based on a study of 300 patients, consists of 2 mg. injected intravenously, to be followed 30 seconds later by an additional 8 mg. if the first portion does not elicit a reaction.

During the past three years in the myasthenia gravis clinic of the Mount Sinai Hospital, New York, we have utilized the edrophonium (Tensilon) chloride test as a diagnostic procedure in over 300 persons referred to us as possibly having myasthenia gravis. The diagnosis of myasthenia gravis was established in 110 of these patients. Thousands of edrophonium tests were performed in the management of these proved cases. Edrophonium chloride, an analogue of neostigmine (Prostigmin), is a rapid-acting cholinergic drug.[1] Because of its short duration of action, edrophonium was found to be suitable for use in the diagnosis of myasthenia gravis.[2] Further study revealed the value of the edrophonium test in the differential diagnosis of myasthenic from cholinergic crisis.[3] This test was also found to be useful as an aid in management of the patient with myasthenia gravis, facilitating regulation of proper dosage of cholinergic drugs.[4] The edrophonium test was further shown to be a valuable aid in estimating the effectiveness and duration of action of experimental drugs made available for the treatment of myasthenia gravis.[5] On the basis of this experience, certain refinements of the edrophonium test are now recommended.

EARLY TECHNIQUE

In original studies [2] the average anticurare dose of edrophonium chloride, 1 cc. (10 mg.), was selected on an empirical basis for the rapid diagnostic test for myasthenia gravis. Edrophonium chloride was administered intravenously in approximately 15 seconds. The patient with myasthenia gravis reacted within approximately 30 to 40 seconds, exhibiting the following response: (1) increased muscle strength when there was previous weakness; (2) marked subjective improvement; (3) minimal to absent side-reactions; and (4) no fasciculations.

In the normal subject, administration of edrophonium chloride causes no change in muscle strength. Fasciculations are almost always noted. (Fasciculations are not present when neostigmine is used as a testing agent. However, the diagnosis with the edrophonium test is not dependent upon the presence or absence of fasciculations alone.) It is important to emphasize that positive responses to edrophonium chloride usually occur within the first one to two minutes of the injection. Within five minutes the patient with myasthenia gravis returns to the pretest status.

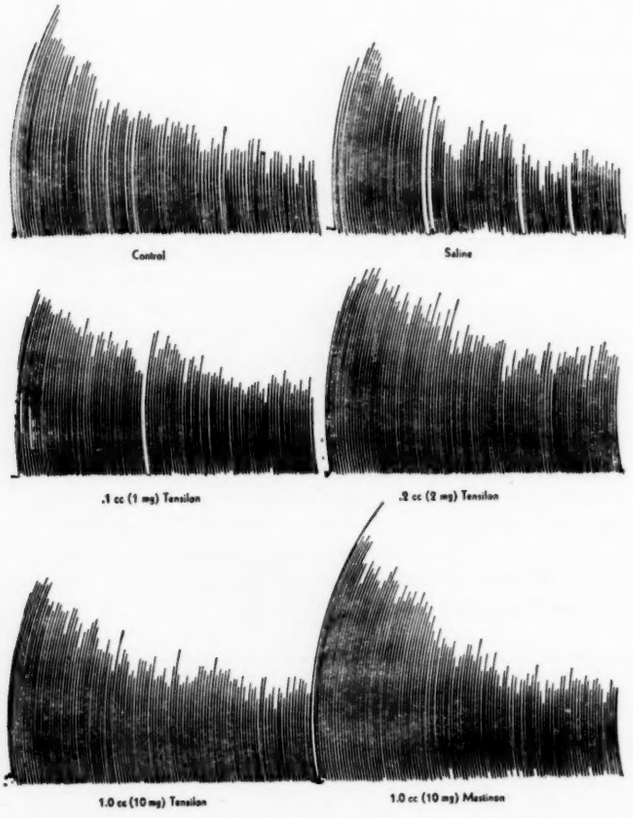
From the Myasthenia Gravis Clinic and the departments of medicine and neurology, the Mount Sinai Hospital.
This study was aided in part by grants from the Myasthenia Gravis Foundation, New York, and Hoffmann-LaRoche, Inc., Nutley, N. J.
The edrophonium chloride used in this study was supplied as Tensilon by Dr. T. C. Fleming of Hoffmann-LaRoche, Inc.

1. Randall, L. O.: Anticurare Action of Phenolic Quarternary Ammonium Salts, J. Pharmacol. & Exper. Therap. **100**: 83, 1950.
2. Osserman, K. E., and Kaplan, L. I.: Rapid Diagnostic Test for Myasthenia Gravis: Increased Muscle Strength, Without Fasciculations, After Intravenous Administration of Edrophonium (Tensilon) Chloride, J. A. M. A. **150**: 265 (Sept. 27) 1952.
3. Osserman, K. E., and Kaplan, L. I.: Studies in Myasthenia Gravis: Use of Edrophonium Chloride (Tensilon) in Differentiating Myasthenic from Cholinergic Weakness, A. M. A. Arch. Neurol. & Psychiat. **70**: 385 (Sept.) 1953.
4. Osserman, K. E.: Kaplan, L. I., and Besson, G.: Studies in Myasthenia Gravis: Edrophonium Chloride (Tensilon) Test as a New Approach to Management, J. Mt. Sinai Hosp. **20**: 165 (Sept.-Oct.) 1953.
5. Osserman, K. E.; Teng, P., and Kaplan, L. I.: Studies in Myasthenia Gravis: Preliminary Report on Therapy with Mestinon Bromide, J. A. M. A. **155**: 961 (July 10) 1954.

FALSE-NEGATIVE RESPONSE

In our series of 110 patients with myasthenia gravis, false-negative responses occurred in 8 patients, with 1 cc. (10 mg.) of edrophonium chloride as the intravenously given diagnostic dose. These eight patients were apparently hyperreactive to edrophonium. They exhibited a cholinergic response with fasciculations and muscarinic side-reactions such as flushing of the face, tearing, salivation, abdominal cramps, nausea, vomiting, and diarrhea. In addition, the weakness of the striated muscles was accentuated. This false-negative response can also be seen after the intravenous or intramuscular injection of a diagnostic dose of neostigmine methylsulfate in subjects hyperreactive to neostigmine.

The false-negative response to edrophonium, neostigmine, or any cholinergic agent employed for the purpose



Serial ergography showing response to injection of increasing increments of edrophonium chloride.

can be explained by the pathological physiology of the disease and the pharmacodynamics of these drugs. The patient is rapidly brought from a myasthenic state into a cholinergic response. This can be accounted for on the basis of drug dosage. By clinical trial, 0.2 cc. (2 mg.) of edrophonium chloride was selected as a testing dose for myasthenia gravis when a cholinergic response was elicited with 1 cc. (10 mg.). Subsequently, graded doses were evaluated by the following technique. Bulb ergograms requiring 105 seconds were recorded by patients known to have myasthenia gravis when they were in need of a dose of therapeutic drug. To establish the proper rest period and to overcome the fatigue of the first test, serial ergograms were performed at various time intervals; thus, a five-minute rest period was sufficient to eliminate this factor. After the patient recorded a control ergogram, a five-minute rest period followed. Saline solution in a tuberculin syringe was injected intravenously and the needle left in site. A 30-second wait is required for a response. A second ergogram is now recorded and another rest period allowed. A second syringe with edrophonium is attached. Increasing increments of edrophonium chloride are injected starting with 0.1 cc. (1 mg.), then 0.2 cc. (2 mg.), 0.4 cc. (4 mg.), and finally 1 cc. (10 mg.), with ergograms and rest periods after each dose (see figure).

The graphs made by patients with myasthenia gravis who were in need of medication showed noticeable improvement after an injection of 0.1 cc. (1 mg.) of edrophonium chloride; after 0.2 cc. (2 mg.) there was only a moderate improvement over the 0.1 cc. test. A plateau was reached at 0.2 cc. (2 mg.), with only slight improvements to 1 cc. (10 mg.). Patients who are hyperreactive to edrophonium demonstrate their best ergogram results with 0.1 cc. (1 mg.), whereas, with 1 cc. (10 mg.) they showed weakness from overdosage. The ergograms of some subjects recorded improvement with the administration of 0.1 cc. (1 mg.) of edrophonium chloride; however, conditions such as ptosis or diplopia were not always completely relieved until 0.2 cc. (2 mg.) or 0.4 cc. (4 mg.) or even 1 cc. (10 mg.) was given.

FALSE-POSITIVE RESPONSE

There is no therapeutic test that is absolutely pathognomonic. Hysteria can simulate almost any symptomatology known. In myasthenia gravis, placebo testing can be done with saline solution, atropine, or a flushing agent such as nicotinic acid. A positive edrophonium test serves to confirm the clinical impression derived from the history and physical examination.

DIFFERENTIAL DIAGNOSIS

Myasthenia gravis may affect any striated muscle in the body. It may involve the bulbar as well as the skeletal musculature and often presents symptoms simulating neurological entities. In many instances the clinical picture may resemble isolated cranial nerve palsies, bulbar paralysis caused by neoplasms, infections, or vascular occlusions, or degenerative processes such as multiple sclerosis. In infants the impression may be the so-called congenital nuclear agenesis. Cases in which weakness appears only in the limb and trunk muscles may simulate muscular dystrophy and peripheral neuropathy or amyotonia congenita. Bulbar myasthenia gravis on occasions has been mistaken for bulbar poliomyelitis with respiratory difficulties. Severe weakness associated with certain forms of hyperthyroidism and periodic familial paralysis must also be considered in the differential diagnosis of myasthenia gravis. We have used the edrophonium test on all of the above conditions, and the response was that of normal individuals, i. e., no change in muscle strength, except in two cases of periodic familial paralysis in which we had to use atropine promptly to counteract severe side-reactions.

An important differential diagnosis exists between myasthenia gravis and psychoneurosis with marked fatigability. Occasionally a psychoneurotic individual will show the improvement of symptoms with edrophonium testing expected from a patient with myasthenia gravis. This occurred in four patients tested. The use of the

placebo test helped to clarify this situation. To remove all doubt in this type of case, it may even be necessary to give the patient a therapeutic trial with neostigmine, Mestinon (a dimethyl carbamate of 3-hydroxy-1-methyl pyridinium bromide), or ambenonium (Mysuran) chloride, formerly known under the research name WIN 8077. Placebo tablets of neostigmine or Mestinon may be used to compare results. An additional aid is the presence of an eye-closure phenomenon that is exhibited by some psychoneurotics tested with edrophonium. This response is an involuntary forcible closure of the eyelids and is often accompanied by marked muscarinic side-reactions. However, it should be noted that the eye closure could be present in psychoneurosis in conjunction with myasthenia gravis. This phenomenon, therefore, must be evaluated on the basis of the over-all findings.

RECOMMENDED TECHNIQUE

A tuberculin syringe containing 1 cc. (10 mg.) of edrophonium chloride is prepared with an intravenous needle; 0.2 cc. (2 mg.) of edrophonium chloride is injected intravenously within 15 seconds and the needle left in site. Only if no reaction occurs after 30 seconds, inject the remaining 0.8 cc. of edrophonium. If cholinergic reaction occurs after injection of 0.2 cc., discontinue test and wait one-half hour; repeat test using 0.1 cc. (1 mg.) of edrophonium chloride.

Dosage for Children.—The intravenously given testing dose of edrophonium chloride in children up to 75 lb. (34 kg.) of body weight is 0.1 cc. (1 mg.). For children above this weight, use 0.2 cc. (2 mg.). Because an intravenous route may be difficult to use for children, the intramuscular route may be used. In children up to 75 lb. of body weight, inject 0.2 cc. (2 mg.) of edrophonium chloride intramuscularly. In children above 75 lb. of body weight, inject 0.5 cc. (5 mg.) intramuscularly.

Intramuscularly Given Test in Adults.—In adults with inaccessible veins, the dose for injection intramuscularly is 1.0 cc. (10 mg.) of edrophonium chloride. In subjects hyperreactive to this dose, wait one-half hour and repeat using 0.2 cc. (2 mg.) edrophonium intramuscularly to rule out false-negative reactions. All signs that would appear with the intravenously given test also appear with the intramuscularly given one, except that there is a delay of 2 to 10 minutes until a reaction takes place. Unlike neostigmine testing, where the effects last for an hour or two, with edrophonium the reaction is worn off within a period of 5 to 10 minutes.

TEST IN CRISIS

Crises with respiratory failure are a major problem in myasthenia gravis. In recent years it has become more apparent that overdosage with cholinergic medication may cause respiratory failure. This has been called cholinergic crisis.[6] It is most important when a patient is in crisis that one establish whether the cause is underdosage or overdosage. The clinical observation made by the physician and the patient must be considered. The edrophonium test is only used in crisis when the history is vague or unobtainable and the physical examination inconclusive. The test reveals that the patient is cholinergic if he becomes momentarily worse. Edrophonium is much less toxic than neostigmine in cholinergic crisis, because edrophonium is short-acting. If neostigmine is used, the patient becomes worse and remains so for one to two hours or more and may require the use of the respirator. We have been able to avoid the use of the respirator in three cases by resorting to the edrophonium test.

If a patient in crisis is placed in a respirator, it is advisable to discontinue cholinergic medication for the first 24 hours. If the patient is cholinergic, this permits effects of the medication to wear off. If the patient is myasthenic, it allows him to live during this period without medication and possibly lowers the resistance to therapeutic agents when they are reinstituted. When drug therapy is resumed, the patient may not be able to talk because of a tracheotomy tube nor write because of weakness. In such instances, we observe the respiration of the patient as the criterion for effectiveness of medication by opening the vents of the respirator. The patient is then given his dose of cholinergic drug. If need be, the adequacy of medication may be tested one hour later by performing an edrophonium test. In respirator cases when the edrophonium test is used, 0.1 cc. (1 mg.) is the initial dose and should be slowly increased by 1 mg. increments until a response is observed.

SUMMARY

Over 300 patients suspected of having myasthenia gravis have been tested with edrophonium (Tensilon) chloride. One hundred ten subjects exhibited a positive response to the test. In our original report, we recommended the use of 1 cc. (10 mg.) of edrophonium chloride as an intravenously given injection for the rapid diagnosis of myasthenia gravis. Although this dose gave positive responses in 93% of the patients tested, there was a small group of hyperreactive subjects in whom this dose was found to be too large; therefore, we advised a new dosage schedule for the edrophonium chloride test in order to avoid the false-negative responses. A tuberculin syringe filled with 1 cc. (10 mg.) of edrophonium chloride is prepared; 0.2 cc. (2 mg.) is injected leaving the needle in site; and, if no reaction occurs after 30 seconds, the remaining 0.8 cc. of edrophonium is injected. If a cholinergic response occurs with 0.2 cc., the test is discontinued. One-half hour later, the test may be repeated using 0.1 cc. (1 mg.).

The intravenously given dosage of edrophonium chloride recommended for children is 0.1 cc. (1 mg.) for those weighing less than 75 lb. (34 kg.) and 0.2 cc. (2 mg.) for children above this weight. The intramuscularly given dosage for children is 0.2 cc. (2 mg.) or 0.5 cc. (5 mg.), depending upon weight. An intramuscularly given dosage of 1 cc. (10 mg.) is recommended for adults. If the subject is hyperreactive, one may repeat the test in one-half hour using 0.2 cc. (2 mg.). False-positive edrophonium tests can be avoided through the use of a placebo injection of either saline solution, atropine, or nicotinic acid prior to the starting of the edrophonium test; results of the placebo and edrophonium tests are then compared. The edrophonium chloride test may be used in crisis when the history is vague or unattainable and the physical examination inconclusive.

4 E. 89th St. (28) (Dr. Osserman).

6. Schwab, R. S.: Belladonna Drugs in Cholinergic Poisoning During Treatment of Myasthenia Gravis, Correspondence, J. A. M. A. **155**: 1445 (Aug. 14) 1954.

TREATMENT OF MYASTHENIA GRAVIS WITH MESTINON BROMIDE

Joseph E. Tether, M.D., Indianapolis

• ***The diagnosis of myasthenia gravis was made in 165 patients whose symptoms were either aggravated by one-tenth of the minimal curarizing dose of tubocurarine chloride or objectively improved by intravenously administered neostigmine. Most patients satisfied both criteria. Mestinon was compared with neostigmine in these patients. Mestinon was effective in controlling the myasthenic symptoms, particularly the dysphagia. Its action was smoother because more prolonged, and no distressing side-effects were observed even in patients who used it as long as 17 months.***

In 1954 I reported [1] preliminary findings in 56 patients with myasthenia gravis who had been treated with Mestinon bromide (a dimethyl carbamate of 3-hydroxy-1-methyl pyridinium bromide). Since then the number of patients who received Mestinon has been enlarged to 165. It is the purpose of this report to describe the experience with this larger group, some of whom were treated for periods as long as 17 months.

PROCEDURE

In order to facilitate the evaluation of results, a numerical code was assigned to the severity of myasthenic symptoms while the patients were under therapy. The same code was used to indicate the reactions to the drug. The numerical designations were as follows: 0, no symptoms; 1, slight; 2, mild; 3, moderate; 4, severe. All of the patients were first observed while receiving neostigmine therapy. Mestinon bromide tablets (60 mg.) were then given orally as a substitute for neostigmine bromide. The initial dose of Mestinon was three to four times that of neostigmine and was subsequently altered, if necessary, according to the clinical indications. All of the patients were either diagnostically aggravated by one-tenth of a minimal curarizing dose of tubocurarine chloride or objectively improved by intravenously administered neostigmine, or in most cases, both.

RESULTS

The table summarizes the results in 165 patients. The duration of the disease ranged from 1 to 50 years (average, 8.2). The period of treatment with Mestinon was 3 to 17 months (average, 10.2). Those patients who were given 1,200 mg. or less of Mestinon daily obtained good control of their symptoms. These results compare favorably with those of the preliminary report (0.6 to 1.2 vs. 1.1). The severity of drug reactions was almost identical with that reported earlier (0.5 to 0.6 vs. 0.4). The 15 patients who required more than 1,200 mg. of Mestinon daily did not have as good control of symptoms as did those in the lower dosage groups. Their average symptoms were 1.6 and 2.9 as compared with 0.6 and 1.2. Indeed, the severity of the myasthenic symptoms regularly increased as the Mestinon requirements grew larger. Interestingly, however, the severity of drug reactions decreased in patients with these larger requirements. One interpretation of these findings is that the dosage of Mestinon should have been greater in some of these patients in order to obtain a further decrease in the myasthenic symptoms. In spite of the fact that one patient took 6,000 mg. per day she had no drug reactions. This phenomenon of increased need of and tolerance for Mestinon in proportion to the severity of myasthenic symptoms has also been observed with neostigmine and other cholinergic drugs.

An analysis of the distribution of patients according to their daily Mestinon dosage shows 33% of the patients took less than 200 mg., 30% took 200 to 399 mg., 29% took 400 to 1,399 mg., and 8% took 1,400 mg. or more. The daily intake of one-third of the patients was approximately three tablets or less of Mestinon. These patients with milder cases, most of whom obtained almost complete relief of symptoms with Mestinon. They are examples of a view I have held for some time, namely, that myasthenia is not a rare disease and that there are many mild-to-moderate cases for every one with the classical severe symptoms of myasthenia gravis. In view of the large number of cases in this series an analysis was made of the Mestinon dosage versus the duration of the disease. No significant correlation was found.

Most of the patients who experienced less improvement with Mestinon than with neostigmine in the preliminary report were retreated with Mestinon. The majority of these have since reported better results with Mestinon than with neostigmine. In most cases their failure to achieve superior results with Mestinon was due to underdosage and in a few to overdosage. One patient apparently did not absorb sufficient Mestinon from her gastrointestinal tract to achieve any effect whatever, so she added 100 tablets of Mestinon (6,000 mg.) to her usual daily dosage of 100 neostigmine tablets (1,500 mg.), without apparent beneficial effect and without side-effects. A few patients who prefer neostigmine during the day take Mestinon on retiring because its effect seems to last through the night better than neostigmine. Almost all patients reported that they were stronger on arising. Many who previously had to take neostigmine throughout the night found that a bedtime dose of Mestinon lasted through the night. This would seem to indicate that Mestinon has a more prolonged effect than neostigmine. A typical example of the longer duration of effect following Mestinon therapy is illustrated in case 1.

REPORT OF CASES

CASE 1.—A 28-year-old white woman was first seen at Robert Long Hospital in September, 1942. She had noted the onset of easy fatigue and weakness of her legs, with frequent falls, about

From the Department of Neurology, Indiana University Medical Center.

The Mestinon bromide used in this study was supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.

Dr. M. J. Schiffrin of Hoffmann-LaRoche, Inc., offered advice and assistance in this study.

1. Tether, J. E.: Mestinon in Myasthenia Gravis: Preliminary Report, Dis. Nerv. System **15**: 227 (Aug.) 1954.

two years previously, followed by ptosis, diplopia, dysarthria, dysphagia, and general weakness. A definite diagnosis of myasthenia gravis was made, and treatment with neostigmine bromide was started. Since then this patient's dosage has averaged about 35 15-mg. tablets (525 mg.) daily, with a maximum of 60 tablets and a minimum of 20. She usually took six tablets every two and a half to three hours during the day and would regularly awaken with choking in the night and take six more. She was always extremely weak on arising and would have difficulty in swallowing her tablets. Nevertheless, she experienced no reactions and was able to carry on her work at various jobs, including management of a dress shop and an insurance office, doing her housework in addition. About a year ago, therapy with Mestinon was started. She found that six tablets every four to five hours was sufficient for improved, "steadier" strength during the day. She was, moreover, surprised when she arose quite strong and able to swallow and realized that she had not awakened during the night and had thus taken no medication since retiring. As reported in the preliminary study, no signs of organic toxicity have been encountered in any patients treated with Mestinon.

Three recent reports on the use of Mestinon have appeared in the American literature.[2] There is a general agreement that Mestinon produces fewer disagreeable gastrointestinal effects than does neostigmine. This enables the patient to take a sufficient amount of medication to overcome some of the symptoms that may not have yielded to neostigmine. According to Osserman and co-workers,[2a] "The effectiveness of Mestinon is only slightly longer than that of neostigmine." Westerberg and Magee [2b] reported, "Mestinon gave a more prolonged effect and more even maintenance of strength than did neostigmine." Schwab and Timberlake,[2c] however, were unable to produce evidence that Mestinon had any longer action than neostigmine. In the preliminary report I indicated that Mestinon is more slowly and evenly absorbed or has a more prolonged duration of activity, or both. My enlarged experience over a significant period of time supports the conclusion that Mestinon has a more sustained and even course of effectiveness than has neostigmine. Osserman [2a] has observed that Mestinon seems more effective than neostigmine on the smaller muscles, innervated by cranial nerves. I have also noted this in many of the patients. Seibert,[3] however, felt that Mestinon was more effective on the larger muscles. Westerberg [2b] noted no difference in this respect, and Schwab [2c] mentioned none. As Schwab warns, increased gastrointestinal tolerance to Mestinon may in some cases present a hazard, as there are thus less early warning symptoms of overdosage. In my experience, Mestinon in excess usually produces, in addition to sweating, salivation, and mild abdominal symptoms, rather definite "nicotinic" side-effects, such as muscle fasciculations, a peculiar blurring or "jumping" of vision with mild vertigo, and, occasionally, a "thick tongue" sensation, with dysarthria and dysphagia. These symptoms are usually accompanied by increased weakness. If they are ignored, and if more medication is taken, this weakness may include the muscles of respiration resulting in a cholinergic crisis, difficult to distinguish from a true myasthenic crisis. Occasionally, cholinergic weakness may precede all other signals of overdosage. This is illustrated in case 2.

Summary of Experience with Mestinon in Treatment of Myasthenia Gravis

	Daily Dose Mestinon Bromide, Mg.			
	240 or Less	241-1,200	1,201-2,400	More Than 2,400
No. of cases	76	74	11	4
Average duration of disease, yr.	8.0	8.0	13.3	1.8
Duration of disease, yr.	1-41	1-50	1-50	1-4
Average duration Mestinon therapy, mo.	10.3	9.8	12.4	11.8
Duration Mestinon therapy, mo.	3-16	3-17	4-16	5-16
Average daily dose, mg.	160	541	1,825	4,325
Daily dose, mg.	60-240	270-1,200	1,300-2,400	3,200-6,000
Average symptoms with therapy*	0.6	1.2	1.6	2.9
Symptoms with therapy*	0-2.5	0-3	0-3	2-4
Average reactions to Mestinon*	0.5	0.6	0.1	0
Reactions to Mestinon*	0-3	0-3	0-1	0

* 0 = no symptoms, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe.

CASE 2.—A 27-year-old white housewife was first seen on March 6, 1953. She complained of ptosis of her eyelids and easy fatigue, with weakness of extremities, neck, and jaws beginning about four years before her first visit. She was three months' pregnant, and this was her third pregnancy. She developed extreme weakness, aggravated ptosis, and blurred vision after administration of 0.3 cc. of tubocurarine chloride given intravenously. Ptosis and weakness disappeared after she was given 0.5 mg. of neostigmine intravenously. The severity of her myasthenia progressed rapidly throughout her pregnancy. The dosage of neostigmine given orally rose from 45 to 450 mg. daily at the time of delivery on Sept. 20, 1953. During delivery, she had a brief respiratory crisis, relieved by 0.5 mg. of neostigmine methylsulfate given intravenously. The child, a 5 lb. 14.5 oz. (4,290 gm.) girl, breathed and cried spontaneously. During the mother's first postpartum month of receiving treatment her neostigmine dosage fell to 300 mg. daily. After this it rapidly rose to 1,110 mg. daily (74 15-mg. tablets) by Nov. 23, 1953. Treatment was then rapidly changed to Mestinon. With therapy with this drug, at a daily dosage of 2,280 mg. (38 60-mg. tablets), she stated that she felt stronger and "steadier." However, in less than a week, her daily dosage had risen to 3,900 mg. (65 tablets), plus two 1 mg. injections of neostigmine methylsulfate. Despite the heavy dosage of both neostigmine and Mestinon, she never experienced any side-effects until Nov. 29, 1953, when, without warning, as she carried her baby upstairs, her legs collapsed and she fell and struck her head. The child was unharmed, but the mother was put to bed. Within 30 minutes, she developed mild abdominal cramping and diarrhea. On the following day she took 1,620 mg. (27 tablets) of Mestinon. Within a month, her daily dosage had dropped to 600 mg. (10 tablets) and by February, 1954, as low as 240 mg. (4 tablets). She has experienced no further side-effects or episodes of cholinergic weakness.

I have seen several other patients with extreme dysphagia who have increased their Mestinon dosage to the point of cholinergic crisis in a desperate attempt to improve deglutition. However, I have seen the same situation occur with neostigmine. In the great majority of cases, symptoms of Mestinon overdosage are clear enough to serve as warning signals, especially if patients are trained to recognize them.

SUMMARY

Mestinon bromide (a dimethyl carbamate of 3-hydroxy-1-methyl pyridinium bromide) was given to 165 patients with myasthenia gravis for periods of from 3 to 17 months (average, 10.2 months). The daily dose in

2. (*a*) Osserman, K. E.; Teng, P., and Kaplan, L. I.: Studies in Myasthenia Gravis: Preliminary Report on Therapy with Mestinon Bromide, J. A. M. A. **155**:961 (July 10) 1954. (*b*) Westerberg, M. R., and Magee, K. R.: Mestinon in the Treatment of Myasthenia Gravis, Neurology **4**: 762 (Oct.) 1954. (*c*) Schwab, R. S., and Timberlake, W. H.: Pyridostigmin (Mestinon) in the Treatment of Myasthenia Gravis, New England J. Med. **251**: 271 (Aug. 12) 1954.

3. Seibert, P.: Treatment of Myasthenia Gravis: Clinical Experiences Concerning Treatment of Pseudoparalytic Myasthenia Gravis with Pyridostigmine, Deutsche med. Wchnschr **78**: 805 (May 29) 1953; abstracted, J. A. M. A. **153**: 175 (Sept. 12) 1953.

this series was 60 to 6,000 mg. One-third of the patients, those with milder cases, required less than 200 mg. daily. No organic toxic effects were noted, regardless of the dosage of Mestinon. I believe use of Mestinon is an advance in the treatment of myasthenia. It is preferred to neostigmine bromide because of its ability to provide effective, smooth control of myasthenic symptoms without distressing side-effects or wide fluctuations in the intensity of the drug's action.

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THE ANTERIOR APPROACH TO THE STELLATE GANGLION

USE WITHOUT A SERIOUS COMPLICATION IN TWO THOUSAND BLOCKS

Daniel C. Moore, M.D.
and
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• ***Injection of a local anesthetic such as tetracaine about the stellate ganglion aids the diagnosis and relieves the symptoms of many functional disturbances in the upper extremity, chest, head, and neck. An anterior, paratracheal approach to the ganglion, here described, has been used in more than 2,000 cases. It is more easily mastered by the physician than are the older anterolateral and posterior approaches.***

The criteria for a satisfactory block are ptosis, enophthalmos, miosis, and localized vasodilation, increase in skin temperature, and anhidrosis. All blocks in this study were satisfactory, and no severe complications occurred.

During the past years there has appeared in the literature an increasing number of articles written by specialists and some general practitioners stressing the attributes of stellate ganglion block for treatment, diagnosis, and prognosis of numerous diseases of the upper extremity, chest, neck, and head.[1] Nevertheless, the severe complications (i. e., pneumothorax, catastrophic systemic toxic reactions from intravascular injection or a total spinal anesthetic), which have a relatively high incidence after the more frequently employed approaches to the stellate ganglion (i. e., the anterolateral, lateral, or posterior paravertebral) have deterred most physicians from using this block. The exclusion of stellate ganglion block from the armamentarium of a physician deprives both the physician and his patient of its usefulness as a therapeutic and diagnostic aid in the practice of medicine (see table).

In 1945 Findley and Patzer [1a] in discussing stellate ganglion block for the treatment of herpes zoster described an anterior (paratracheal) approach to the stellate ganglion that differed significantly from the above-noted approaches. After reading this article we began to use the anterior (paratracheal) approach to the stellate ganglion because we, too, found that other approaches were difficult for our residents to master, caused pain during execution when the patient had received no medication, and had a relatively high incidence of severe complications. During the past 10 years while using this approach in over 2,000 cases we have made some modifications that in our opinion have further assured the avoidance of the afore-mentioned problems.[2] It is the purpose of this paper to: (1) describe the technique that has been used at the Mason Clinic in over 2,000 blocks without a serious complication and (2) emphasize that this very valuable block procedure is safe and feasible for a physician to use if the technique described herein is very carefully followed.

From the Department of Anesthesia, the Mason Clinic.
Read before the Section on General Practice at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 8, 1955.

1. (*a*) Findley, T., and Patzer, R.: The Treatment of Herpes Zoster by Paravertebral Procaine Block, J. A. M. A. **128**: 1217-1219 (Aug. 25) 1945. (*b*) Caldwell, G. A.; Broderick, T. F., and Rose, R. M.: Sympathetic Block of the Stellate Ganglion: Its Application in Orthopaedic Conditions, J. Bone & Joint. Surg. **28**: 513-520, 1946. (*c*) Amyes, W. E., and Perry, S. M.: Stellate Ganglion Block in the Treatment of Acute Cerebral Thrombosis and Embolism: Report of 44 Cases, J. A. M. A. **142**: 15-20 (Jan. 7) 1950. (*d*) Coston, T. O.: Ocular Symptoms of Stellate Ganglion Block, Its Use in the Treatment of Occlusion of the Central Retinal Artery, Am. J. Ophth. **34**: 1289-1293, 1951. (*e*) Adams, J. E.: Editorial, Stellate Ganglion Block, Surg. Gynec. & Obst., **93**: 369-371, 1951. (*f*) Swan, D. M., and McGowan, J. M.: Shoulder-Hand Syndrome Following Myocardial Infarction: Treatment by Procaine Block of the Stellate Ganglion, J. A. M. A. (June 30) **146**: 774-777, 1951. (*g*) Swan, D. M.: Stellate Block in Bell's Palsy, ibid. **150**: 32-33 (Sept. 6) 1952. (*h*) Gordon, E. J.: Stellate Ganglion Block in Treatment of Bursitis and Tendinitis of the Shoulder, South M. J. **45**: 1131-1138, 1952. (*i*) Carle, H. W.: Stellate Ganglion Block in the Treatment of Various Syndromes Encountered in Cardiovascular Disorders, J. Missouri M. A. **49**: 663-667, 1952. (*j*) Fish, C. A., and Granthan, E. G.: Relief of Pain in Acute Myocardial Infarction by Procaine Block of the Sympathetic Nerve Supply, Ann. Int. Med. **36**: 172-177, 1952. (*k*) Pierach, A., and Stotz, K.: Die Behandlung des Lungenödems mit Novocain-Blockaden des rechten Ganglion stellatum, Deutsche med. Wchnschr. **77**: 1344-1346, 1952. (*l*) Player, G. S.: Block Treatment of Stroke, Northwest Med. **52**: 116-118, 1953. (*m*) Gilbert, N. C., and de Takats, G.: Cervical Sympathetic Block, J. A. M. A. **152**: 870-871 (June 27) 1953. (*n*) Walsh, R. C.: Stellate Ganglion Block in General Practice, Brit. M. J. **2**: 684-685, 1954.

2. Moore, D. C.: Stellate Ganglion Block: Techniques, Indications, Uses, Springfield, Ill., Charles C Thomas, Publisher, 1954.

TECHNIQUE

Position and Landmarks.—The patient lies in the dorsal recumbent position without a pillow and with his arms at his sides. The head is tilted backward so the neck is in maximum extension (fig. 1). This straightens the esophagus and makes its anatomic relationship in the neck constant. An X is made 1¼ in. (3.2 cm.) to 1½ in. (3.8 cm.), approximately two fingerbreadths, lateral to the jugular notch of the sternum and the same distance above the clavicle (fig. 1). This landmark should lie over the transverse process of the seventh cervical vertebra and along the medial border of the sternocleidomastoid muscle. The cephalad edge of the stellate ganglion lies at approximately this level (fig. 2).

The patient is now instructed to turn his head to the side opposite the one being blocked, and the carotid

(Chassaignac's) tubercle, the anterior tubercle of the transverse process of the sixth cervical vertebra, is located. This is easily done by placing the fingers behind the lateral border of the sternocleidomastoid muscle and feeling for the most prominent transverse process. An O is placed on the skin overlying the sixth transverse process along the medial border of the sternocleidomastoid muscle (fig. 1). The cricoid cartilage is palpated and marked (fig. 1). This usually lies at the level of the transverse process of the sixth cervical vertebra, the exception being in a thin, long-necked patient. These two anatomic structures serve as a check on the seventh

Conditions in Which Block of Cervical and Upper Thoracic Portions of Sympathetic Nervous System May Be of Value (After Moore [2])

		1. Traumatic vascular occlusion 2. Thrombophlebitis 3. Postoperative edema 4. Raynaud's disease 5. Ischemic paralysis (Volkmann's, etc.) 6. Shoulder-hand syndrome 7. Idiopathic neuralgias 8. Causalgia 9. Bursitis
	Upper extremity and upper chest wall (T_1-T_4)	10. Herpes zoster 11. Cervical rib 12. Amputation pain 13. Phantom sensations 14. Frostbite 15. Osteoporosis 16. Nonunion of fractures 17. X-ray dermatitis 18. Scleroderma
I. Conditions associated with vascular disturbances	Brain	1. Cerebral accidents 2. Spasm from angiography
	Heart	1. Angina pectoris 2. Myocardial infarcts
	Lung	1. Embolism 2. Acute edema 3. Hemoptysis
	Face	1. Facial (Bell's) palsy 2. Herpes zoster 3. Neuralgias 4. Occlusion of retinal artery
II. Increased glandular secretions	Hyperhidrosis Bronchorrhea	
III. Bronchiolar spasm (asthma)		
IV. Abnormal cardiac rhythm		

transverse process, which was marked with an X and which should lie approximately ½ in. (1.3 cm.) below the O and the cricoid cartilage marking the sixth transverse process (fig. 1).

Precautions.—The landmarks should be carefully checked to be sure they are not more than 1¼ in. (3.2 cm.) to 1½ in. (3.8 cm.) from the midline of the jugular notch of the neck. The patient's head should be fully extended at all times while the procedure is being carried out. This maneuver straightens the slight normal curve to the left of the esophagus. The patient should be instructed not to talk, cough, or move while the injection is being made. These instructions should be repeated as the needle is being inserted. At all times during the procedure, a full 10-cc. syringe should be securely attached to the Lok-needle to facilitate injections and prevent possible dislodgment of the needle. Careful aspiration for blood or spinal fluid is imperative.

Procedure.—The area is aseptically prepared and draped. The anesthetist stands on the side of the patient, facing the patient. An intradermal wheal is raised at the determined X with the ¾ in. 25-gauge Huber point

Fig. 1.—Patient in position for a stellate ganglion block by the anterior (paratracheal) approach. Note extension of the head. The topographical anatomy is indicated. X lies over the transverse process of the seventh cervical vertebra, O marks the sixth cervical transverse process, and the line marked C the cricoid cartilage. (This and the following illustrations are from Moore.[2])

security Lok-needle. If the anesthesiologist is right-handed, the full 10-cc. Lok-syringe, with the 1½ in. (3.8 cm.) or 2-in.(5 cm.) security Lok-needle attached, is held in the right hand while the index and middle fingers

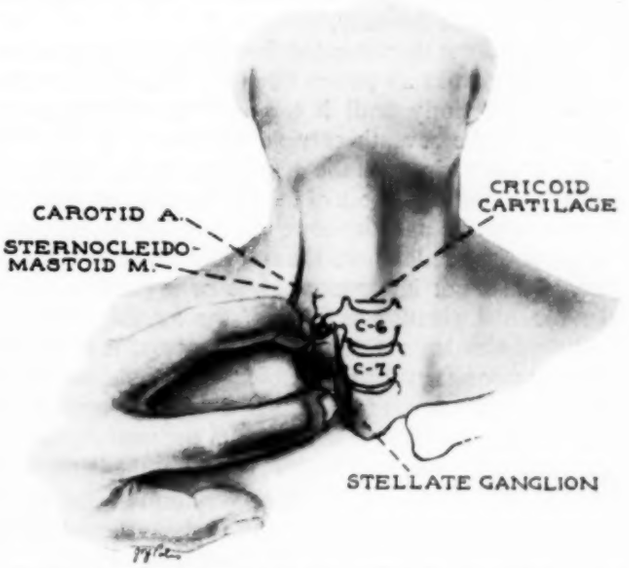

Fig. 2.—The fingers act as retractors, pulling the sternocleidomastoid muscle and carotid sheath laterally.

of the left hand straddle the X mark on the neck (fig. 2 and 3). Downward and lateral pressure is exerted with the fingers of the left hand so that the sternocleidomastoid muscle and carotid sheath are pulled laterally (fig. 2 and

3). It is important that the pulsation of the carotid artery be felt on the lateral side of the depressing fingers. The left hand holds this position until the block is completed. No attempt should be made at this time to palpate the transverse processes with either the index or the middle

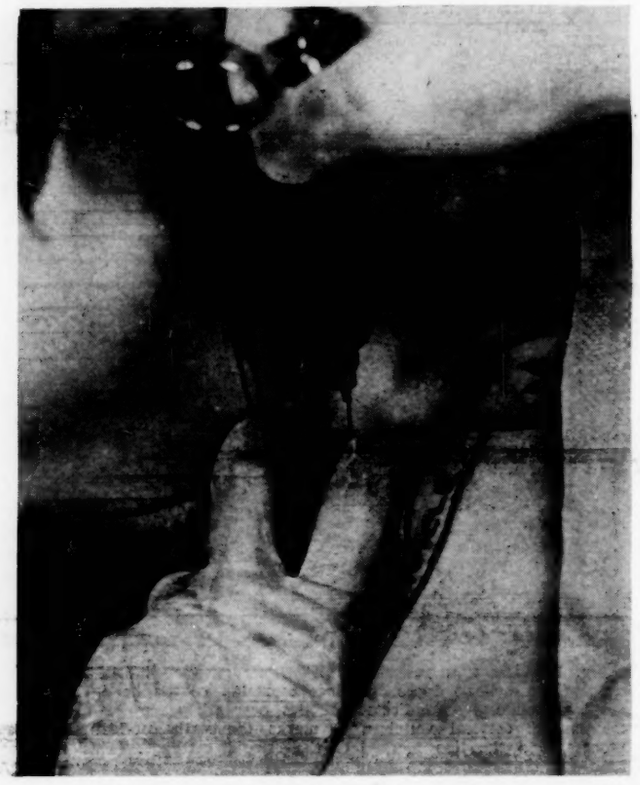

Fig. 3.—Anterolateral view of needle as it is being inserted perpendicular to the skin over the seventh cervical transverse process. Note position of index and middle fingers pulling the sternocleidomastoid and carotid sheath with its vessels and nerves laterally.

fingers of the left hand. The straddling fingers act merely as retractors to pull the carotid sheath and sternocleidomastoid muscle laterally.

The needle is then inserted through the X perpendicular to the skin in all planes (fig. 3). Then it is pushed slowly posteriorly until it impinges on the transverse process of the seventh cervical vertebra (fig. 4). The exact depth varies with the depression of the skin by the index and middle fingers of the left hand as well as with the build of the patient; however, it is seldom necessary to insert the needle more than 1½ in. If, however, the needle does not impinge on bone or if paresthesias of the brachial plexus are elicited, the needle should be withdrawn and reinserted so that the point is more medial. If bone is still missed, then the needle should be pointed either caudad or cephalad until it impinges on the transverse process. It is seldom necessary to adjust the needle. After the needle rests on the transverse process of the seventh cervical vertebra, it should be withdrawn ⅛ in. (0.3 cm.) to free it from the substance of the muscles that lie over the transverse process.

A careful aspiration test is done for blood or spinal fluid. If either appears, the needle must be adjusted before injection. If neither appears, 1 to 2 cc. of the solution is injected and 15 to 30 seconds allowed to pass. If no reaction occurs, the contents of the syringe are discharged. The needle is then withdrawn.

The test dose of 1 to 2 cc. is injected because, occasionally, although no blood is obtained on careful aspiration, the needle may rest in a blood vessel, usually the vertebral artery. If this is true, 1 to 2 cc. of the blocking agent will produce dizziness, the feeling of "blacking out," and nausea within this time, because of the cerebral manifestations of the drug. When 1 to 2 cc. of the drug is not exceeded, a severe systemic toxic reaction with loss of consciousness seldom occurs. If the above signs and symptoms are elicited, the injection should be stopped. The needle should be withdrawn from the lumen of the vessel, moved laterally, and contact made with the anterior root rather than with the posterior root of the transverse process of the seventh cervical vertebra before continuing the injection. The use of a test dose is stressed because intravascular injection into the vertebral artery is a distinct possibility with this approach, and, if a large quantity of the local anesthetic solution (10 to 15 cc.) is injected, a severe systemic toxic reaction could result.

RESULTS

All of the blocks cited herein were deemed satisfactory. The criteria for a satisfactory block were the appearance of Horner's syndrome (ptosis, enophthalmos, and miosis) and the signs of sympathetic block in the upper extremity (vasodilatation of the superficial veins, increase in skin temperature, and anhidrosis). There have been no pneumothoraxes, subarachnoid (spinal) injections, severe systemic toxic reactions, deaths, or asthmatic attacks during use of this technique.

As with any procedure in medicine, some minor complications have been observed. In six instances blood was obtained by aspiration prior to injecting the local anesthetic solution. In five cases, although no blood could be obtained by aspiration, the injection of the test dose of the local anesthetic solution (1 to 2 cc.) pro-

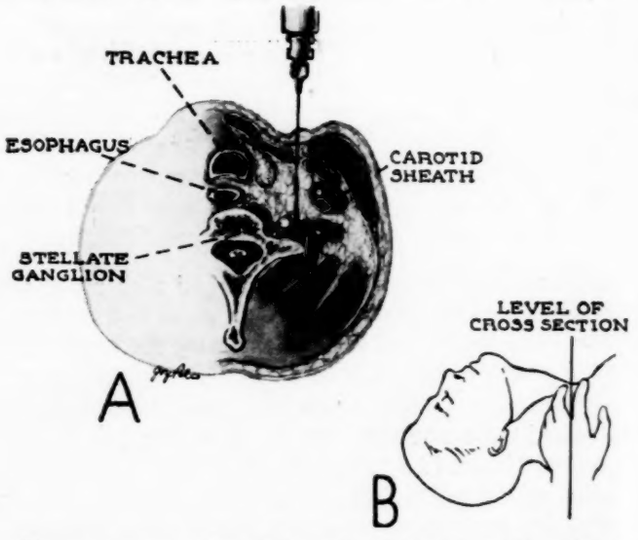

Fig. 4.—*A*, cross section of the neck showing the needle resting on the seventh cervical transverse process. Note the effects of downward pressure and lateral traction on the carotid sheath. *B*, level of cross section.

duced dizziness, ringing in the ears, and the feeling of "blacking out"—symptoms of injection of the local anesthetic drug into the vertebral artery. Although no blood could be obtained after another attempt at aspiration was made, the above symptoms were conclusive evi-

dence that the point of the needle rested inside the lumen of a vessel. Thus the injection of a test dose had probably averted a severe systemic toxic reaction. In these 11 cases the needle was removed from the vessel's lumen, an adjustment of it was made as described previously, and the block was satisfactorily executed.

In two cases the patient complained of numbness of both arms following the injection of the local anesthetic solution. This numbness lasted from two to four hours and then disappeared. The plausible explanation of this would be the injection of the local anesthetic solution into the epidural space. With the exception of the numbness, the patient complained of no other untoward reaction. In 5 to 8% of the blocks we have noted that hoarseness accompanies the block. In less than 3% of the cases partial brachial plexus anesthesia has occurred. These two minor complications are corrected as the local anesthetic agent is dissipated.

ADVANTAGES

We do not wish to delve into the indications for stellate ganglion block. The purpose of this paper is to emphasize the anterior approach to the ganglion with our modifications—not give an entire dissertation on the diseases that may be treated by it. Suffice it to list them (see table) and to say that most conditions that benefit from the therapeutic use of stellate ganglion block require a series of blocks, i. e., 6 to 10 blocks rather than one individual block. Since a series of blocks is necessary in most cases to improve the condition being treated, a technique for a stellate ganglion block, if it is to be used frequently, must (1) be easily executed without causing the patient much pain; (2) be free of severe complications; (3) result in a satisfactory block in a high percentage of cases; and (4) be easy to master.

Absence of Pain During Execution.—Since it is necessary in most instances to perform 6 to 10 blocks for optimal results, most of the patients with conditions in which a stellate ganglion block is indicated must be treated as office patients. The cost would preclude treatment with stellate ganglion block if one of the requirements for its execution was hospitalization. Because most of these patients are not hospitalized—the exception being the patient who is hospitalized for the disease, per se—they are usually not sedated for the block. In our experience the anterior approach to the stellate ganglion has not produced sufficient pain to deter patients from returning daily or weekly for injection. If a large number of patients are willing to continue their treatment and do not complain that the procedure is painful, we can assume that the pain associated with the technique is minimal.

Absence of Severe Complications.—Since many of the patients treated by stellate ganglion block therapy are outpatients, it is necessary to avoid, if possible, pneumothoraxes, high spinal anesthesia, and severe systemic toxic reactions to the local anesthetic agent. These complications cause the patient to lose confidence in the technique and the physician's ability and in some instances may require hospitalization with increased expense. The anterior approach to the stellate ganglion seems to avoid these severe complications. It is interesting to note that Orkin, Papper, and Rovenstine [3] in reporting their complications with the various approaches to the stellate ganglion had no complications when they employed the anterior (paratracheal) approach; however, with the anterolateral or the posterior approaches, severe complications were cited.

Minor complications, such as those noted under the section on results, will cause the patient no concern provided he is cautioned that these might occur and that they will be corrected in a matter of a few hours as the local anesthetic solution is dissipated. If hoarseness occurs, the patient should be instructed not to eat or drink while it is present. Hoarseness indicates that the vocal cords, the "watchdog" of the trachea, are partially ineffective, and when they are in this condition food or fluid may enter the trachea. While no severe complications have occurred in this series of cases, resuscitation equipment and drugs (i. e., means of giving oxygen by bag and mask, intravenous fluids, airways, vasoconstrictor drugs, suction, and short-acting barbiturates) have been immediately available.

High Incidence of Satisfactory Results.—As mentioned previously, all blocks in this study were successful with this technique; however, in occasional instances we have had to repeat the procedure if the desired results were not accomplished by the first injection. With the anterior approach we found that the patient seldom objected to immediate reinjection because of the simplicity and brevity of the block as well as absence of pain.

Some have condemned the anterior approach to the stellate ganglion when treating conditions of the upper extremity because they contend that there are instances when most of the sympathetic fibers of the upper extremity do not pass through the stellate ganglion but go directly to the arm via the brachial plexus and the vascular system. Therefore, they advocate the posterior approach to the stellate ganglion when treating conditions of the upper extremities. To date we have not failed to find the signs of an adequate sympathetic block of the upper extremity following the anterior approach. Also, it should be stressed that, irrespective of the approach to the stellate ganglion, a block of the entire cervicothoracic portion of the sympathetic nervous system, not just the stellate ganglion, occurs, providing 10 cc. to 15 cc. of the blocking solution is used and the needle is correctly placed.[2] This has been conclusively demonstrated by one of us [2] and Alexander [4] employing iodopyracet (Diodrast) solutions. In all of our cases it is routine to check for sympathetic denervation of the upper extremity before and after the block. It must be stressed that Horner's syndrome may occur and yet the signs of a sympathetic nerve block of the upper extremity may be absent. If this is the case and the block was performed for a disease of the upper extremity or chest wall, the block should be repeated with each step in the technique being performed more carefully.

In all the blocks in this series, 10 cc. to 15 cc. of 0.25% tetracaine (Pontocaine) hydrochloride, with or without 0.1 cc. of epinephrine hydrochloride 1:1,000,

3. Orkin, L. R.; Papper, E. M., and Rovenstine, E. A.: The Complications of Stellate and Thoracic Sympathetic Nerve Blocks, J. Thoracic Surg. **20**: 911-922, 1950.

4. Alexander, F. A. D., and Lovell, B. K.: Roentgenologic Control of Nerve Blocks: Use of Iodopyracet Injection (Diodrast), J. A. M. A. **148**: 885-886 (March 15) 1952.

was the anesthetic solution of choice because of its long duration of action; however, other local anesthetic solutions of the physician's own liking may be used.

Quick Mastery.—In order for a block procedure of this type to become a part of the armamentarium of many physicians it must produce a satisfactory block in a high percentage of cases for the physician learning the technique and for the physician who has occasion to employ it infrequently as well as for the physician who has become skilled in its execution through constant usage. In our attempt to evaluate the efficiency of the anterior approach we selected it as the method of choice for teaching our residents in anesthesia and have been most gratified with the results. After instruction along with the first two to three blocks we found the residents were able to perform the technique often with a dexterity equal to that of the instructor.

In addition, we have shown the technique to a number of vascular surgeons in our community. These men were performing a large number of stellate blocks in their offices and were using either the anterolateral or the posterior approach. It was interesting to note that after these physicians had used the anterior approach a number of times they volunteered the information that they would not return to the other approaches because they found that the anterior approach could be executed with little or no pain and that severe complications were absent. The above findings have led us to concur with Smith [5] who noted that the anterior (paratracheal) approach avoids the complications of stellate ganglion block common to other methods and that this approach is readily mastered by those least adept.

It should be cautioned that alcohol injection of the stellate ganglion should not be done by the anterior approach. The anterior approach relies on the spread of 10 to 15 cc. of the local anesthetic agent in the correct fascial plane. This quantity of alcohol cannot be safely injected in this area, since with alcohol the minor complications that have been noted under the section on results might last for six to nine months and be a source of annoyance to both the patient and the physician.

SUMMARY AND CONCLUSIONS

From the results of 2,000 stellate ganglion blocks with the anterior approach, it is concluded that it is the best approach for executing such a block with a local anesthetic agent. The anterior (paratracheal) approach avoids the complications of stellate ganglion block common to other methods, and this approach is readily mastered by those least adept. The technique is simple from the standpoint of both the physician and the patient. Severe complications with use of this technique did not occur in this series.

1115 Terry Ave. (1) (Dr. Moore).

5. Smith, D. W.: Stellate Ganglion Block: The Tissue Displacement Method, Am. J. Surg. **82**: 344-348, 1951.

USE OF BENZATHINE PENICILLIN G IN CARRIERS OF GROUP A BETA-HEMOLYTIC STREPTOCOCCI

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• A single injection of 600,000 units of benzathine penicillin G was given intramuscularly to each of 2,913 recruits whose throat cultures had yielded beta-hemolytic streptococci. In 624 of these cases the streptococci were classified as group A, and the single injection of antibiotic resulted in negative cultures for at least one month thereafter in 597 cases. No control group was provided, but it is significant that rheumatic fever did not occur in any recruit who had received an injection of 600,000 units of the antibiotic.

Unfavorable reactions, which generally consisted of rash and urticaria, occurred in 25 cases, and only one of these was considered serious. Benzathine penicillin G merits further investigation as a possible single-injection prophylactic agent for the control of streptococcic infections.

Primary infections due to beta-hemolytic streptococci and the nonsuppurative complications of these infections constitute one of the most important epidemiological problems in the armed forces.[1] It now seems clear [2] that the early institution of antibiotic therapy is effective in altering favorably the clinical course of disease resulting from infections with group A streptococci. It has been further demonstrated [3] that the administration of adequate amounts of penicillin is effective in eradicating the carrier state. Seal and co-workers [4] have pointed out that the administration of 250,000 units of penicillin given orally twice daily may be expected to terminate abruptly an epidemic of streptococcic infections and to prevent the development of rheumatic fever, when administered to all members of an involved population.

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1. (*a*) Denny, F. W., and others: Prevention of Rheumatic Fever: Treatment of Preceding Streptococcic Infection, J. A. M. A. **143**: 151-153 (May 13) 1950. (*b*) Department of Preventive Medicine, Surgeon General's Office, cited by Denny and others.[1a]

2. (*a*) Footnote 1*a*. (*b*) Prevention of Rheumatic Fever and Acute Nephritis by Early Penicillin Treatment of Hemolytic-Streptococcus Infections, editorial, New England J. Med., **242**: 1025-1028 (June 29) 1950. (*c*) Chamovitz, R.; Catanzaro, F. J.; Stetson, C. A., and Rammelkamp, C. H., Jr.: Prevention of Rheumatic Fever by Treatment of Previous Streptococcal Infections: Evaluation of Benzathine Penicillin G, ibid. **251**: 466-471 (Sept. 16) 1954. (*d*) Brock, L. L., and Siegel, A. C.: Studies on the Prevention of Rheumatic Fever: The Effect of Time of Initiation of Treatment of Streptococcal Infections on the Immune Response of the Host; J. Clin. Invest. **32**: 630-632 (July) 1953. (*e*) Weber, R. W., and Seal, John R.: Antibiotic Treatment of Streptococcal Exudative Tonsilitis or Pharyngitis in Navy Recruits, Research Project NM 005 051.10.02, Navy Bureau of Medicine and Surgery, Department of Defense, 1954.

They found, however, that within two weeks after prophylaxis with this dosage, new cases of streptococcic infections began to appear. This observation on the importance of long-continued administration of penicillin in the prophylactic treatment of streptococcic sore throat and rheumatic fever has been substantiated by others.[5]

In 1952 Stollerman and Rusoff [6] reported the successful use of a long-acting injectable penicillin preparation, benzathine penicillin G (Bicillin), in the prevention of recurrences of streptococcic infections in a group of 135 children and 8 adults who were known rheumatic subjects. This study indicated that effective blood levels were often maintained for as long as four weeks after a single intramuscular injection of 1,200,000 units of benzathine penicillin G. During the period of this study, there was no instance of a recurrence of rheumatic fever in any of the patients receiving regular dosages of this preparation. There has been speculation [6] that the maintenance of effective penicillin levels in the blood and tissues for long periods of time might result in more severe and more prolonged reactions to this drug in the event that such reactions appeared. Available data on this point are inconclusive, but preliminary studies do not appear to substantiate it. The value to the armed forces of an effective single-injection, long-term preparation is apparent, and, to further investigate the use of benzathine penicillin G, the following study was undertaken at the U. S. Naval Training Center, Bainbridge, Md., between Oct. 15, 1953, and May 4, 1954. It has been reported [6] that injections of benzathine penicillin G in amounts of 1,200,000 units produce considerable pain at the site of injection, to the extent that some patients may be incapacitated. It was partly because of this observation that a smaller amount (600,000 units) was administered in the present study.

MATERIALS AND METHODS

The physical facilities and the recruit population at the training center in Bainbridge, Md., have been described.[3c] During the winter months routine throat cultures were made on all recruits of the First Regiment. With few exceptions these surveys were made at biweekly intervals. During the same period of time recruits of the Fourth Regiment were examined weekly or biweekly, and cultures were taken of all men with clinical evidence of pharyngitis. New companies entering the two regiments were examined on the first day of their schedule. Cultures were read 16 to 18 hours after plating, and all individuals from whom a beta-hemolytic Streptococcus organism was obtained were given 600,000 units of benzathine penicillin G intramuscularly in the gluteal region within 24 hours after the throat culture was made, excluding those men with a history of previous penicillin sensitivity. In this manner, a total of 2,696 men received a single injection of benzathine penicillin G. Two hundred seventeen additional recruits also received at the same time an injection of 600,000 units of procaine penicillin G. All beta-hemolytic streptococci obtained from the throat cultures were grouped by the capillary precipitation technique of Swift and coworkers,[7] and 673 cultures were found to contain group A streptococci. Recruits were not routinely admitted to the sick list unless they had clinical symptoms sufficient to warrant it. Most of the men, therefore, who were given benzathine penicillin G were not placed under observation in the hospital, and for this reason it is not unlikely that minor reactions to the drug went undetected. It must also be stated that records of subsequent therapy were not available, and it is probable that a few recruits may have received additional antibiotics or other medicaments at routine sick call.

RESULTS

The number of recruits receiving 600,000 units of benzathine penicillin G intramuscularly in whom throat cultures were positive for beta-hemolytic streptococci was as follows: First Regiment, 2,204; Fourth Regiment, 437; and new companies, 272. The effectiveness of the dosage in eradicating beta-hemolytic streptococci from the throat is presented in table 1. Only those persons in whom at least two throat cultures were taken after the administration of the benzathine penicillin G were considered to have had an adequate follow-up study. Positive cultures obtained after the fourth week, with at least two negative cultures after treatment, were considered as reinfections. Positive cultures occurred in 10 men between the fourth and sixth weeks, and an additional 11 men had positive cultures only eight weeks after treatment.

TABLE 1.—*Effect of Benzathine Penicillin G in Eradicating Beta-Hemolytic Streptococci from the Throat*

	No.	%
Total no. with positive throat culture given drug...	673	....
Incomplete follow-up study.....	49	....
Total no. with adequate follow-up study.....	624	100.0
Streptococcus eradicated from throat *.....	597 †	95.6
Positive culture obtained in less than 2 wk.....	17	2.7
Positive culture only after 2 wk.....	10	1.6

* At least 2 negative cultures between 14 and 28 days after treatment.
† Positive cultures obtained from 10 of these men between 4th and 6th week after treatment and from 11 after only 8 weeks.

It was repeatedly noted that from week to week positive cultures were obtained from individuals who previously had negative cultures. This was taken as evidence that the streptococci were being transmitted from person to person. Generally speaking, the maximum pe-

3. (*a*) Brink, W. R.; Rammelkamp, C. H., Jr.; Denny, F. W., and Wannamaker, L. W.: Effect of Penicillin and Aureomycin on the Natural Course of Streptococcal Tonsilitis and Pharyngitis, Am. J. Med. **10**: 300-308 (March) 1951. (*b*) Denny, F. W.; Wannamaker, L. W., and Hahn, E. O.: Comparative Effects of Penicillin, Aureomycin and Terramycin on Streptococcal Tonsilitis and Pharyngitis, Pediatrics **11**: 7-13 (Jan.) 1953. (*c*) Seal, J. R.; Mogabgab, W. J.; Friou, G. J., and Banta, J. E.: Penicillin Prophylaxis of Epidemic Streptococcal Infections: I. The Epidemic and the Effects of Prophylaxis on the Clinical Manifestations of Acute Streptococcal and Nonstreptococcal Respiratory Infections, J. Lab. & Clin. Med. **44**: 727-753 (Nov.) 1954; II. The Effects of Small and Large Doses of Oral Penicillin on Epidemic Streptococcal Infections and on Carriers of Group A Streptococci, ibid. **44**: 831-859 (Dec.) 1954.

4. Footnote 3*c*. Seal, J. R.: Oral Penicillin Prophylaxis of Streptococcal Infections, Am. J. Pub. Health **45**: 662-672 (May) 1955.

5. Footnote 2*e*. Haight, T. H.: Controlled Studies on the Comparative Efficacy of Erythromycin and Penicillin in the Treatment of Scarlet Fever, Research Project NM 005 051.10.01, Navy Bureau of Medicine and Surgery, Department of Defense, 1954. Massell, B. F.; Dow, J. W., and Jones, T. D.: Orally Administered Penicillin in Patients with Rheumatic Fever, J. A. M. A. **138**: 1030-1036 (Dec. 4) 1948.

6. Stollerman, G. H., and Rusoff, J. H.: Prophylaxis Against Group A Streptococcal Infections in Rheumatic Fever Patients: Use of New Repository Penicillin Preparation, J. A. M. A. **150**: 1571-1575 (Dec. 20) 1952.

7. Swift, H. F.; Wilson, A. T., and Lancefield, R. C.: Typing Group A Hemolytic Streptococci by M Precipitin Reactions in Capillary Pipettes, J. Exper. Med. **78**: 127-133 (Aug.) 1943.

riod of dissemination occurred between the fourth and sixth weeks of recruit training, though this was not always the case. In some companies 10 or more positive cultures were obtained from men who previously had had one or more negative cultures. Thus, it appears that conditions were favorable for the dissemination of streptococci. It therefore seems notable that 576 of the 624 men in the study had no recurrences during the remainder of their recruit training. None of these individuals was studied for less than four weeks or had less than two cultures taken after the administration of benzathine penicillin G. The significance of these findings is not entirely clear, since, during the time of this study, there was a very low incidence of clinical streptococcic pharyngitis at the training center, with no recruits being hospitalized with this diagnosis. The fact, therefore, that such a small number of the recruits to whom benzathine penicillin G was administered had subsequent positive cultures for group A beta-hemolytic streptococci seems to indicate a period of protection against this organism of perhaps four to six weeks. There was no case of rheumatic fever in any recruit who received an injection of 600,000 units of the drug.

TABLE 2.—*Reactions After Injection of Benzathine Penicillin G*

	No.	%
Total no. receiving drug	2,913	100.0
Total no. with reactions	25	0.86
Type of reactions		
Rash	8	32.0
Fever	3	12.0
Immediate (within 48 hr.), including hives and urticaria. Interval not known in 1 case	6	24.0
Delayed (appearing after 48 hr.), including hives, urticaria, edema, lymphadenopathy, painful joints, purpuric reaction. Interval not known in 2 cases	19	76.0
Average no. of days before onset of reaction (all types). Not known in 2 cases	8.39	....
No. hospitalized	8	32.0
Total hospital days (all patients)	66	....
No. who had taken penicillin before	10	40.0
No. with previous penicillin sensitivity	..	....
No. with any type of allergy	1	4.0

REACTIONS

Of the 2,696 recruits who were given single injections of 600,000 units of the drug, and the additional 217 men who received the benzathine penicillin G plus procaine penicillin G, 25, or 0.86%, reported to sick call with complaints and findings considered to be reactions to penicillin. Data on these individuals are summarized in table 2. Ten of these men had a history of having previously taken penicillin without a reaction. No reactions of the anaphylactic type were encountered, and those that are included in table 2 under the designation "Immediate reaction" appeared within the first 48 hours. The usual interval before onset of reactions in these cases was one to four hours, though, in one instance, urticaria appeared on the upper and lower extremities two days after the injection. Reactions appeared on the fifth day in two of the individuals classed as having "Delayed reaction," and in the remainder of cases the interval was 8 to 14 days.

Eight of the men were hospitalized for a total of 66 hospital days, but three of these patients accounted for 49 of these days. Only one severe reaction was encountered, and there was some considerable doubt that this man actually had a penicillin reaction. He reported to sick call 25 days after injection of benzathine penicillin G complaining of generalized rash, chills, and swollen, painful joints. He was hospitalized for 25 days, during which time the diagnosis of rheumatic fever was investigated and ruled out. As a therapeutic test he was given an additional injection of penicillin, with marked exacerbation of his symptoms and signs. Another patient exhibited a generalized purpuric reaction, which appeared within 48 hours after the administration of penicillin. This patient had very limited symptomatology and stated that he came to sick call only because he was disturbed by the appearance of skin lesions. He was not hospitalized, and the lesions disappeared in approximately one week.

COMMENT

It appears from the results that benzathine penicillin G may warrant further investigation as a safe, effective, long-term, single-injection prophylactic agent in the control of streptococcic infections and their nonsuppurative sequelae. It further appears that a single injection of 600,000 units may be highly effective in eradicating group A streptococci from the throat and in preventing reinfection for approximately one month. The reaction rate encountered is based upon a tabulation of those recruits who voluntarily reported to sick call. No effort was made to ferret out men with minor symptoms and signs that might have been related to penicillin administration. The rate obtained (0.86%) is therefore not all-inclusive. Though the importance of minor reactions should not be underestimated, it seems not inappropriate to base reaction data on a consideration of only those men who had sufficient symptoms and/or signs to prompt them to seek treatment. Seal and co-workers [3c] have shown that prophylaxis with orally given penicillin results in approximately 0.3% reactions. There is some indication, therefore, that the number of reactions may be slightly higher after the injection of benzathine penicillin G than after the administration of orally given penicillin, but, from these observations, the reactions do not appear to be more severe or of a longer duration. The use of frequent throat cultures followed by the administration of benzathine penicillin G is not suggested as a practical approach to the control of epidemic streptococcic disease in large military populations. It should also be noted that the data presented here do not constitute a study on the prevention of rheumatic fever, since no control group was provided. They do appear to indicate the need for additional investigation.

SUMMARY

Throat cultures made on recruits of the U. S. Naval Training Center, Bainbridge, Md., during the winter of 1953-1954 yielded 2,913 cultures positive for beta-hemolytic streptococci. Each man was given 600,000 units of benzathine penicillin G (Bicillin) intramuscularly within 24 hours after the culture was made. Six hundred twenty-four of the cultures were found to contain group A streptococci and were obtained from men who were followed for at least four weeks, with no less than two additional cultures taken between the second and fourth weeks after treatment. Five hundred ninety-

seven had negative cultures thereafter for at least one month, and 576 had no known recurrence for the remainder of their recruit training. Reactions to the drug occurred in only 25, or 0.86%, of the men. These were mostly of a mild, transient nature. The most commonly observed lesions were rash and urticaria. These studies suggest that benzathine penicillin G may be a suitable agent for mass prophylaxis against infections due to group A streptococci and that further investigation is warranted.

PORPHYRIA AND PREGNANCY

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• ***The passing of red urine, leading to the diagnosis of porphyria, provided the essential clue in three cases marked by attacks of pain and many severe neurotic and psychotic symptoms. In one the abdominal pain had led to a fruitless laparotomy; in another the neuropsychiatric disorder had made institutional care necessary. The patients were all women who had gone through two or more pregnancies.***

The etiology of porphyria is uncertain, and treatment is primarily symptomatic. In the present cases, however, barbiturates were possible contributing causes, and treatment by intravenous administration of tetraethylammonium chloride gave encouraging results in one case.

Porphyria is a metabolic disorder manifested by a marked overproduction of uroporphyrin and related substances. There are instances when porphyria may occur as a sequela to some other disease or condition. Pregnancy has been observed in association with porphyria, and a fatal relapse of the disease has been reported to have occurred in a patient at the time of delivery, although there is no definite evidence that the relapse was due to pregnancy.[1] There are only a few cases of porphyria associated with pregnancy in the literature. Because of this small number, a review of the literature is presented and three additional cases are reported. Porphyria was first described by Gunther in 1911, and his classification of the disease, used for years, is as follows: (1) congenital, (2) acute, and (3) chronic porphyria. This terminology, however, is conflicting because it is somewhat overlapping in character. A recent and more basic classification by Schmid is as follows: (1) porphyria erythropoietica (photosensitive, Gunther's congenital) and (2) porphyria hepatica—intermittent (Gunther's acute or toxic) and mixed (Gunther's chronic).[2]

DESCRIPTION OF DISEASE

Photosensitive porphyria (erythropoietica or congenital) is rare. The onset is early in life, either prenatal or postnatal. Hydroa vacciniforme with eventual scarring and mutilation of exposed skin, as well as erythrodontia, may occur. Splenomegaly and hemolytic anemia occur occasionally, and splenectomy may relieve the symptoms and cause the porphyria to become latent, with disappearance of photosensitivity. Acute toxic porphyria (hepatica) of the intermittent type is relatively common, especially in women. This is the type of porphyria that the obstetrician and gynecologist is most likely to encounter. Patients with this type of porphyria have abdominal pain that frequently simulates that of an acute abdomen. Often, peripheral neuropathy is present and the patients experience anesthesias and paresthesias in various parts of the body. Vasomotor phenomena may be present. Varying neuropsychiatric disturbances such as weakness, paralyses, hysterical behavior, or psychotic episodes may occur. Pigmentation of the skin is present in some cases. Porphobilinogen is usually present in the urine, at least during attacks. The mixed (chronic) type of porphyria is relatively uncommon. Photosensitivity usually appears late in the disease, and the course of the disease is relatively benign. Liver disease with functional impairment is frequent, and the patient may also have attacks of abdominal pain; however, neuropsychiatric disturbances are infrequent.[2]

The psychiatric syndrome that seems to be present in all cases of porphyria can be divided into three phases. The intermittent phase occurs between acute attacks but, although the patient is free of physical symptoms and the urine is free of abnormal quantities of porphyrins, she may show an altered personality characterized by hysteria, egocentricity, and anxiety in crowds. The prodromal phase may not always occur, as the patient may go directly from the intermittent into the toxic phase. During the prodomal phase the patient may have definite accentuation of neurotic symptoms that may be noted by persons in contact with the patient but that are not severe enough to cause the seeking of medical aid. Toward the end of this phase the patient may have stubborn constipation and vague abdominal pain and cramps. The toxic phase is characterized by acute abdominal pain and a fulminating neurological picture—a true toxic psychosis, during which time the patient may have auditory and visual hallucinations, marked depression and suicidal tendencies, and convulsive seizures of a generalized Jacksonian type. Fulminating ascending paralyses of the Landry type have been noted to occur.[3]

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1. Watson, C. J.: Porphyria, in Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment, Duncan, G. G., editor, ed. 3, Philadelphia, W. B. Saunders Company, 1952, pp. 1079-1103.
2. Watson, C. J.: Some Recent Studies of Porphyrin Metabolism and Porphyria, Lancet **1**: 539, 1951.
3. Olmstead, E. G.: The Neuropsychiatric Aspects of Abnormal Porphyrin Metabolism: Clinical Study, J. Nerv. & Ment. Dis. **117**: 300, 1953.

CHEMISTRY AND PHYSIOLOGY

Because of the predominance of neurological and psychiatric symptoms that are present in porphyria, a short review of the chemistry and physiology is presented, in an attempt to correlate the signs and symptoms of the disease with the pathological findings. Porphyrins are pigments that possess a basic structure of four pyrrole rings linked by methene bridges and that are found throughout the vegetable and animal kingdom. Actinoporphyrin is the basic pigment in chlorophyll, and protoporphyrin is the basic pigment in blood. Porphyrins are also components of vital enzyme systems such as the cytochromes.[4] Hans Fischer in 1915 first described, named, and isolated in crystalline form the uroporphyrins and coproporphyrins. According to Kluver, porphyrin occurs in man in its pure state only in the white matter of the brain, the spinal cord, and the cranial nerves that have more than a purely motor function.[4a] Patchy degeneration of the myelin sheath of the peripheral nerves and degenerative changes in the autonomic ganglions, especially in the celiac axis, have been described.[5] Coproporphyrin and uroporphyrin may be found in feces and urine in small amounts, probably derived from ingested plant and animal tissues. There is no evidence that they come from hemoglobin breakdown, but, since they are found in developing red blood cells, it is believed that they are associated with erythropoiesis.[2]

The liver appears to be the organ of excretion of porphyrins. Five to 10 mcg. of uroporphyrin and coproporphyrin is usually excreted in the urine and feces during one day. When in pathological amounts, urinary coproporphyrin causes the color of the urine to vary from Burgundy red to almost black. Urinary coproporphyrin may also be excreted as a colorless precursor which, on exposure to sunlight or a chemical reducing agent, converts to the colored pigment. Porphobilinogen originally was thought to be this precursor, or chromogen, but recent studies show that it may be separated from a non-Ehrlich-reacting chromogen and, on heating, is converted only to porphobilin. The finding of uroporphyrin and porphobilinogen in the urine is almost diagnostic of porphyria.[2] Porphobilinogen is easily detected by the use of Watson's modification of the Ehrlich reaction. This test is done by taking equal amounts of urine and Ehrlich's reagent and adding an equal amount of sodium acetate. Three cubic centimeters of chloroform is added, which carries down the soluble salt of urobilinogen and leaves the red insoluble salt of porphobilinogen in the supernatant fluid.

4. Footnotes 1 and 2.

4a. Kluver, cited by Watson.[1]

5. Kehoe, E. L.; Newman, S., and Chandler, B. F.: Acute Porphyria: A Problem in Medical Diagnosis. U. S. Armed Forces M. J. **4**: 1119, 1953.

6. Coleman, R. R.: Acute Porphyria, J. South Carolina M. A. **44**: 117, 1948.

7. Freedman, A.; Yeagley, J. D., and Brooks, J. B.: Acute Porphyria with Improvement During and Following Pregnancy, Ann. Int. Med. **36**: 1111, 1952.

8. Linas, S.; Solomon, M. L., and Figge, F. H. J.: Chronic Porphyria Complicated by Pregnancy, J. A. M. A. **133**: 105 (Jan. 11) 1947.

9. Meyer, H.; Nadler, S. B., and Bloch, T.: Acute Porphyria and Pregnancy, Obst. & Gynec. **3**: 214, 1954.

10. Klieger, J. A., and Meyer, J. M.: Personal communication to the author.

REVIEW OF LITERATURE

The incidence of porphyria associated with pregnancy is low. On reviewing the literature, the following five cases were found. It will be noted that abdominal pain and colored urine are the two prominent findings. Watson reported a case in which the mother died in relapse eight days after delivering a healthy baby. The infant's urine was of a port wine color and contained uroporphyrin and excessive coproporphyrin, but it rapidly became quite normal. This suggests that a considerable transfer of these substances across the placenta might have occurred, although the infant may have formed them.[1] Coleman [6] had a patient with acute porphyria who developed severe symptoms in the first trimester that diminished during the remainder of the pregnancy. She was symptom-free nine months after delivery, at which time he reported the case. She had orange-colored urine for two years prior to pregnancy and also at the time of reporting the case.

Freedman [7] reported on a patient who was severely ill for 10 months and who had a remission, during which time she became pregnant. Severe symptoms returned during the first trimester, but remarkable clinical improvement occurred during the remainder of the pregnancy and delivery. She had been symptom-free for the two years after delivery, at the time of reporting, even though she did occasionally have discolored urine. Linas [8] reported a case of photosensitive porphyria with skin manifestations aggravated by pregnancy and with relief after delivery, even though there was abnormally high excretion of porphyrins in the puerperium. Meyer [9] had a patient whose onset of symptoms occurred after an attempted abortion. There was a positive family history for porphyria in this case. Since porphyria is a relatively uncommon disease and the occurrence of pregnancy in association with porphyria is very rare, the following three cases are presented.

REPORT OF CASES

CASE 1.—A 28-year-old patient delivered her second child by cesarean section on Oct. 12, 1952. During the puerperium the patient received large doses of secobarbital (Seconal) and allyl-isopropyl-acetyl-carbamide (Sedormid), in addition to aspirin and codeine, for generalized arthralgia and myalgia. She was hospitalized on two occasions for three days each in December for nausea, vomiting, and pain. In mid-December, the patient suffered a three day period of auditory and visual hallucinations, at which time she was transferred to a neuropsychiatric hospital. Red urine was noted on Dec. 12 and for the following 10 days. Urinalysis at this time was positive for porphyrins. The patient had residual symptoms of generalized paresthesia and numbness, confined primarily to the trunk and proximal portions of the extremities. Diagnosis was intermittent acute porphyria. In February, 1953, the patient was in complete remission.[10]

CASE 2.—A 33-year-old gravida 11, para 7, abortus 4 female came to the outpatient department of our hospital in June, 1953, because of pain from an incision hernia. Examination revealed a very obese woman with a very tender hernia at the site of a previous right paramesial incision and an intrauterine pregnancy of approximately five months' gestation. A herniorrhaphy was performed on July 20, 1953, and omentum was found adherent to the wall of the sac. She continued to have abdominal pain postoperatively and was thought to be going into labor, but frequent examinations disproved this. The patient was transferred to the gynecologic section for further examination. In reviewing her old charts, it was noted that the urine had been slightly positive for porphyrins in 1951. A repeat urinalysis was positive for uroporphyrins, coproporphyrins, and porphobilinogen. The pa-

tient had been hospitalized in 1951 to determine the cause of a persistent diarrhea; she was also pregnant at that time. A laparotomy performed a short time after delivery revealed tuberculosis of the cecum, and a resection of the terminal ileum, cecum, and ascending colon was executed; the patient was placed on a protracted course of therapy with aminosalicylic acid (PAS) and streptomycin. Tuberculosis had not been found since that time. The patient improved without treatment and was discharged from the hospital in July, 1953.

Two months after the herniorrhaphy, the patient was readmitted to the hospital with an exacerbation of the psychiatric syndrome. She felt nervous and wanted to commit suicide. She had visual and auditory hallucinations, especially at night. Fear of crowds and the feeling that something was wrong with everybody else became pronounced. She had complaints of formication and varying degrees of anesthesia over the entire right side of her body. She also had photophobia. She was treated with tetraethylammonium chloride with good results and was discharged from the hospital after several days. She delivered at term a male infant on Nov. 6, 1953, after which time she complained of abdominal cramps "different than after pains" and was again treated with tetraethylammonium chloride with good results. This therapy had to be repeated three days later. Urinalyses on Nov. 9 and 10 were positive for uroporphyrins and coproporphyrins but negative for porphobilinogen. Her urine was discolored on two separate occasions during the time from diagnosis of porphyria to delivery of her child. The child's urine was checked on May 12, 1954, and was negative for porphyrins. On May 26, 1954, the patient's urine was slightly positive for uroporphyrin and coproporphyrin but negative for porphobilinogen. She continues to have minor neuropsychiatric symptoms at the time of reporting.

CASE 3.—A 34-year-old gravida 4, para 3 female delivered her last child on July 28, 1954, at our hospital. She reentered the hospital on Aug. 22, 1954, with the provisional diagnosis of endometritis. Examination failed to substantiate this or any pelvic pathology. The patient had many neurotic symptoms and her condition was difficult to evaluate. A test of the urine for porphyrins was done, and it was positive for uroporphyrins and coproporphyrins and slightly positive for porphobilinogen. Subsequent tests were negative. The patient had had a laparotomy in June, 1953, because of acute abdominal pain, thought to be a result of endometriosis and adenomyosis. At surgery, the uterus was found to be grossly normal and was not removed; no pathological findings explained her pain. The patient is now being followed in the outpatient clinic for further attacks or symptoms.

TREATMENT

The treatment of porphyria has been primarily on a symptomatic basis. Barbiturates are often found to be the precipitating cause and therefore should be avoided. Chloral hydrate and meperidine (Demerol) hydrochloride have been used to control the pain with fair success. Calcium, vitamin E, crude liver extract, neostigmine, ergotamine tartrate, and corticotropin (ACTH) have been used with varied success.[11] Tetraethylammonium chloride also has been used, and this therapy proved successful with the patient in case 2. The regime used was 300 mg. of tetraethylammonium chloride in 300 cc. of 5% glucose in distilled water, given intravenously at 150 drops per minute. The patient must be watched for signs of hypotension.

COMMENT

The success of tetraethylammonium chloride in the treatment of porphyria causes speculation as to the etiology of the disease. This drug is a ganglionic blocking agent producing interruption of nerve transmission at sympathetic and parasympathetic ganglions. Sympathetic ganglions in patients with porphyria frequently reveal lesions at autopsy, and spasmodic contractions of the intestine found at operation on patients with porphyria have been attributed to these lesions. Porphyrin, in sufficient concentration, causes contraction of isolated intestinal strips in experimental animals.[12] Spasm of the intestine could be the cause of the abdominal pain so often present in cases of porphyria.[5] Becker states that porphyrins in porphyria may have a role similar to uric acid in gout. There may be an interference with the synthesis and release of acetylcholine.[13]

Pain in the extremities, which is present in many cases of porphyria, is often due to peripheral neuropathy. It could also be postulated that the pain is due to vasomotor phenomena such as in Raynaud's disease. Tetraethylammonium chloride has been used with success in the treatment of Raynaud's disease, apparently due to the vasodilatation caused by the sympathetic blocking effect of the drug. There is no proof that pregnancy causes an exacerbation in latent cases of porphyria. In the three cases reviewed the patients had exacerabations in their first trimester, with improvement during the remainder of their pregnancies. Another patient had relief only after delivery. Two of the patients presented developed their symptoms after delivery. The medications used during labor, delivery, and the puerperium could well have been the precipitating cause in these two cases.

SUMMARY AND CONCLUSIONS

A high index of suspicion is needed for diagnosis of porphyria. The psychiatric syndrome is the common denominator, being present to some degree in all phases of porphyria. A patient who has neurotic or psychotic behavior and who has abdominal pain with no localizing signs should be checked for porphyria, especially if she passes red urine. Latent cases of porphyria may be aggravated by the medication used during or after labor and delivery. Tetraethylammonium chloride is one of the drugs of choice in the treatment of porphyria.

ADDENDUM

Since writing this paper, the patient in case 3 reentered the hospital four times because of abdominal pain; however, she signed her release three times prior to the completion of her studies. The last admission was on Feb. 14, 1955, and pain was accompanied by urinary retention. A test of the urine for porphyrins was positive for uroporphyrins and coproporphyrins and for porphobilinogen. She continued to have porphobilinogen in the urine for one week, after which the urine became negative. She was treated with tetraethylammonium chloride and her symptoms improved. A fourth case of porphyria associated with pregnancy was diagnosed after completion of this paper.

CASE 4.—A 27-year-old gravida 4, para 2, abortus 1 female entered our hospital on Feb. 17, 1955, with the symptoms of nausea and vomiting and severe abdominal pain. The Friedman test was positive, and urinalysis for porphyrins was positive for uroporphyrins, coproporphyrins, and porphobilinogen. This patient had been hospitalized eight times during a previous pregnancy in 1953 for a total of 135 days because of hyperemesis gravidarum. She had three hospital admissions after

11. Wehrmacher, W. H.: New Symptomatic Treatment for Acute Intermittent Porphyria, A. M. A. Arch. Int. Med. **89**: 111 (Jan.) 1952.
12. Goldman, A. M., and Kaplan, M. H.: Acute Porphyria, Ann. Int. Med. **34**: 415, 1951.
13. Becker, I. M.: Neuropsychiatric Manifestations of Porphyria: Review of the Literature, Am. Pract. & Digest Treat. **2**: 657, 1951.

delivery because of pernicious vomiting. During this time, she also had mental symptoms severe enough to cause her admission to the psychiatric ward of the hospital but was found to be mentally clear. In 1954, the patient had been hospitalized with the diagnosis of criminal abortion, incomplete. A dilatation and curettage was performed. Four weeks later she was readmitted because of vomiting. Her discharge diagnosis then was psychoneurosis. After the diagnosis of porphyria was made, the patient received a course of tetraethylammonium chloride on two successive days, with poor results. By Feb. 25, 1955, her urine was negative for porphyrins, and the patient was discharged on March 7, symptomatically improved. She was readmitted on March 11 because of severe vaginal hemorrhage. Examination revealed two large, actively bleeding vaginal ulcers, a result of insertion of potassium permanganate tablets into the vagina in an attempt to abort herself. The tests for porphyrins and porphobilinogen were again positive, and remained so for over two weeks. She was given chlorpromazine (Thorazine) hydrochloride parenterally to control the severe nausea and vomiting with good results. She was discharged from the hospital under the care of her private doctor.

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LEVALLORPHAN (LORFAN) AND ALPHAPRODINE (NISENTIL) IN ANESTHESIA

STUDY OF EFFECTS IN SUPPLEMENTATION OF NITROUS OXIDE–OXYGEN–THIOPENTAL (PENTOTHAL) SODIUM ANESTHESIA

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• Nitrous oxide–oxygen–thiopental anesthesia can be supplemented by injections of alphaprodine, an analgesic that reduces the amount of thiopental needed. Alphaprodine in large doses has the disadvantage of causing marked respiratory depression, but this can be prevented by levallorphan. In this study 852 patients who received nitrous oxide, oxygen, thiopental, and alphaprodine with levallorphan were compared with 756 patients who, in a previous study, had received the same combination without levallorphan. The use of alphaprodine reduced the amount of thiopental needed. The addition of levallorphan made it possible to increase the alphaprodine to such a level that in 92 cases of extraperitoneal surgery satisfactory operating conditions were obtained without any thiopental at all. The amount of thiopental needed, in milligrams per minute, diminished as the duration of the anesthesia increased. The same was found to be true for alphaprodine.

During the last decade potent analgesics have been used intravenously for supplementation of nitrous oxide–oxygen–thiopental (Pentothal) sodium anesthesia on an ever-widening scale. The purpose of this supplementation is the reduction of the thiopental requirements for maintenance of adequate general anesthesia and a more rapid postoperative recovery of consciousness. To serve this purpose best, the analgesic should combine rapid onset and short duration of action with safety and satisfactory potency. Because of its relatively short duration of action, meperidine (Demerol) hydrochloride has been used most frequently for the supplementation of nitrous oxide–oxygen–thiopental anesthesia. It has been shown recently, however, by Siker and others [1] that the milligram per minute dose of thiopental necessary for the supplementation of nitrous oxide–oxygen anesthesia could be further reduced and the percentage of patients who reacted to stimulation at termination of surgery significantly increased if small intravenously given doses of alphaprodine (Nisentil) hydrochloride were used instead of meperidine.

Alphaprodine, a piperidine derivative (1,3-dimethyl-4-phenyl-4-propionoxy-piperidine), which is closely related to meperidine (fig. 1), was synthesized by Ziering and Lee in 1947. On a molar basis, alphaprodine is 2.5 to 3 times as potent as meperidine and its duration of action is considerably shorter. The effects of an average therapeutic dose (20 to 30 mg.) of alphaprodine injected intravenously last about 45 minutes. Like all other potent analgesics, alphaprodine when used in large doses causes marked respiratory depression, in general affecting respiratory rate more than tidal volume.[2] Therefore, it is not surprising that attempts to reduce the thiopental requirements further by the use of larger alphaprodine doses invariably resulted in severe respiratory depression.[1]

Since studies by two of us and Sikers [2] in unanesthetized patients had shown that the narcotic antagonist, levallorphan (*l*-3-hydroxy-N-allylmorphinan) tartrate, offers considerable protection against respiratory depression caused by use of alphaprodine, it occurred to one of us (L. A. P.) that the combined use of alphaprodine and levallorphan for supplementation of nitrous oxide–oxygen–thiopental anesthesia might make it pos-

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Read in the Symposium on New Agents and Methods for Analgesia and Anesthesia before the Section on Anesthesiology at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 8, 1955.

The alphaprodine (Nisentil) hydrochloride and levallorphan (Lorfan) tartrate used in this study were supplied by Hoffmann-La Roche, Inc., Nutley, N. J.

1. Siker, E. S.; Foldes, F. F.; Pahk, N-M., and Swerdlow, M.: Nisentil (1,3, Dimethyl-4-Phenyl-4 Propionoxy Piperidine): A New Supplement for Nitrous Oxide-Oxygen, Thiopentone (Pentothal Sodium) Anaesthesia, Brit. J. Anaesth. **26**: 405-410 (Nov.) 1954.

2. Swerdlow, M.; Foldes, F. F., and Siker, E. S.: The Effects of Nisentil HCl (Alphaprodine HCl) and Levallorphan Tartrate on Respiration, Am. J. M. Sc. **230**: 237-250 (Sept.) 1955.

sible to use larger amounts of alphaprodine without producing respiratory depression and thus reduce further, or eliminate, the thiopental requirements. This seemed desirable because of the slow rate of degradation of thiopental in the body that was demonstrated by Brodie and others.[3]

Levallorphan has the same structural relationship to levorphanol (Levo-Dromoran) tartrate (*l*-3-hydroxy-N-methylmorphinan tartrate dihydrate) as nalorphine to

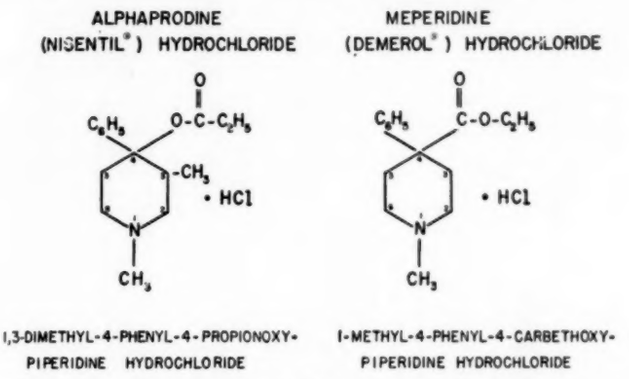

Fig. 1.—Structural formulas showing chemical relationship between alphaprodine (Nisentil) hydrochloride and meperidine (Demerol) hydrochloride.

morphine (fig. 2). Levallorphan was synthesized by Schnider and Grüssner [4] and its animal pharmacology first studied by Fromherz and Pellmont [5] and by Benson and others.[6] Fraser and Isbell [7] investigated the effects of levallorphan in addicts and "postaddicts." Other investigators [8] reported their experiences with levallorphan in anesthetized and unanesthetized patients and in normal subjects under various experimental conditions. The narcotics included in these studies were levorphanol tartrate, morphine, and meperidine.

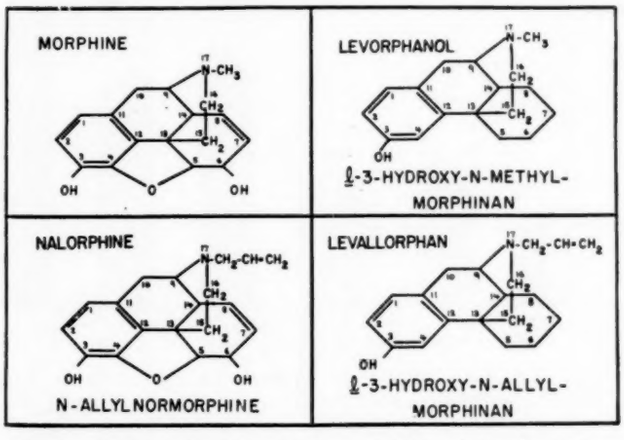

Fig. 2.—Structural formulas showing chemical relationship between narcotic analgesics morphine and levorphanol and their antagonists nalorphine and levallorphan.

As mentioned, Swerdlow and others [2] investigated the action of levallorphan on respiratory depression caused by alphaprodine in unanesthetized persons. Levallorphan in doses of 0.01, 0.02, and 0.04 mg. per kilogram of body weight was administered before, together with, or after administration of 1.0 mg. per kilogram of alphaprodine, both given intravenously, to 210 unanesthetized subjects. It was found that with all three sequences of administration and at all three dose levels, levallorphan afforded considerable protection against the effects of alphaprodine on respiration (fig. 3). The protective action was more marked against the depression of respiratory depth than against that of respiratory rate. As far as could be determined by clinical observations, the administration of levallorphan did not seem to counteract the hypnotic or analgesic effects of alphaprodine. Since the 0.04 mg. per kilogram dose of levallorphan given alone caused approximately 20% depression of respiratory rate and minute volume, the 0.02 mg. per kilogram dose was selected for use in combination with alphaprodine in the present study.

MATERIAL

Alphaprodine and levallorphan were used for supplementation of nitrous oxide–oxygen–thiopental anesthesia in 852 patients; 50 of these were outpatients. In a control series of 756 patients, previously described,[1] alphaprodine alone had been administered as a supplementing agent. Depending on the use of a muscle relaxant during anesthesia, both series were further divided into three subgroups. Patients in the first subgroups did not receive a muscle relaxant, those in the second subgroups were given a relaxant for intubation only, and those in the third subgroups received a muscle relaxant throughout anesthesia (table 1).

TABLE 1.—*Classification of Patients with Reference to Type of Supplementation and Use of Muscle Relaxant*

	No. of Patients Receiving	
	Alphaprodine Plus Levallorphan	Alphaprodine Alone
No muscle relaxant	344	290
Relaxant for intubation	138	145
Relaxant for maintenance	370	321
Total	852	756

The age and sex distributions, as well as the types of operations and the relative frequency of the various procedures, were about the same in both series. With the exception of 82 patients who were anesthetized by one of us (M. S.) at Salford Royal Hospital of Manchester, England, all anesthesia was induced at Mercy Hospital of Pittsburgh.

3. Brodie, B. B., and others: The Fate of Thiopental in Man and a Method for Its Estimation in Biological Material, J. Pharmacol. & Exper. Therap. **98**: 85-96 (Jan.) 1950.

4. Schnider O., and Grüssner, A.: Oxy-morphinane (3. Mitteilung): Optisch aktive 3-Oxy-morphinane, Helvet. chim. acta **34**: 2211-2217, 1951.

5. Fromherz, K., and Pellmont, B.: Morphinantagonisten, Experientia **8**: 394-395 (Oct. 15) 1952.

6. Benson, W. M.; O'Gara, E., and Van Winkle, S.: Respiratory and Analgesic Antagonism of Dromoran by 3-Hydroxy-N-Allyl Morphinan, J. Pharmacol. & Exper. Therap. **106**: 373 (Dec.) 1952.

7. Fraser, H. F., and Isbell, H.: Morphine Antagonists, Fed. Proc. **14**: 340 (March, pt. 1) 1955.

8. (*a*) Gross, E. G., and Hamilton, W. K.: Preliminary Observations on the Effect of Levallorphan on Respiratory Depression and Analgesia of Levorphan in Man, J. Lab. & Clin. Med. **43**: 938-941 (June) 1954. (*b*) Hamilton, W. K., and Cullen, S. C.: Effect of Levallorphan Tartrate upon Opiate Induced Respiratory Depression, Anesthesiology **14**: 550-554 (Nov.) 1953. (*c*) Hamilton, W. K., and Cullen, S. C.: Supplementation of Nitrous Oxide Anesthesia with Opiates and a New Opiate Antagonist, ibid. **16**: 22-28 (Jan.) 1955. (*d*) Cullen, S. C., and Santos, C. C.: Analgesia for Chronic Pain Without Respiratory Depression, A. M. A. Arch. Surg. **69**: 410-414 (Sept.) 1954. (*e*) Thomas, D. V., and Tenney, S. M.: The Effect of Levorphan and Levallorphan on the Respiratory Mechanism of Normal Man, J. Pharmacol. & Exper. Therap. **113**: 250-255 (March) 1955. (*f*) Landmesser, C. M.; Formel, P. F., and Converse, J. G.: Comparative Effects of a New Narcotic Antagonist (Levallorphan Tartrate) upon the Respiratory Responses to Carbon Dioxide During Narcotic and Barbiturate Depression in Anesthetized Man, Anesthesiology **16**: 520-535 (July) 1955.

ANESTHETIC MANAGEMENT

The anesthetic management of the patients in the control series has been described previously.[1] In the present study, patients were given premedication with 50 to 100 mg. of pentobarbital (Nembutal) sodium administered orally or intramuscularly 90 to 120 minutes before surgery and with a combination of 5 to 10 mg. of morphine sulfate, or 50 to 100 mg. of meperidine, and 0.3 to 0.4 mg. of scopolamine hydrobromide administered subcutaneously 45 to 60 minutes prior to induction of anesthesia. On arrival in the operating room, the patient's mouth and pharynx were sprayed with a 1% tetracaine (Pontocaine) hydrochloride solution and an intravenous infusion was started. All subsequent injections were administered through the rubber sleeve of the infusion tubing.

Early in the study, alphaprodine and levallorphan were administered by alternate methods, namely, premixed or separately. With both methods the dose of levallorphan was 0.02 mg. per kilogram of body weight and that of alphaprodine 1 mg. per kilogram (1:50 ratio), except in older, debilitated patients to whom one-half or two-thirds of these doses were given.

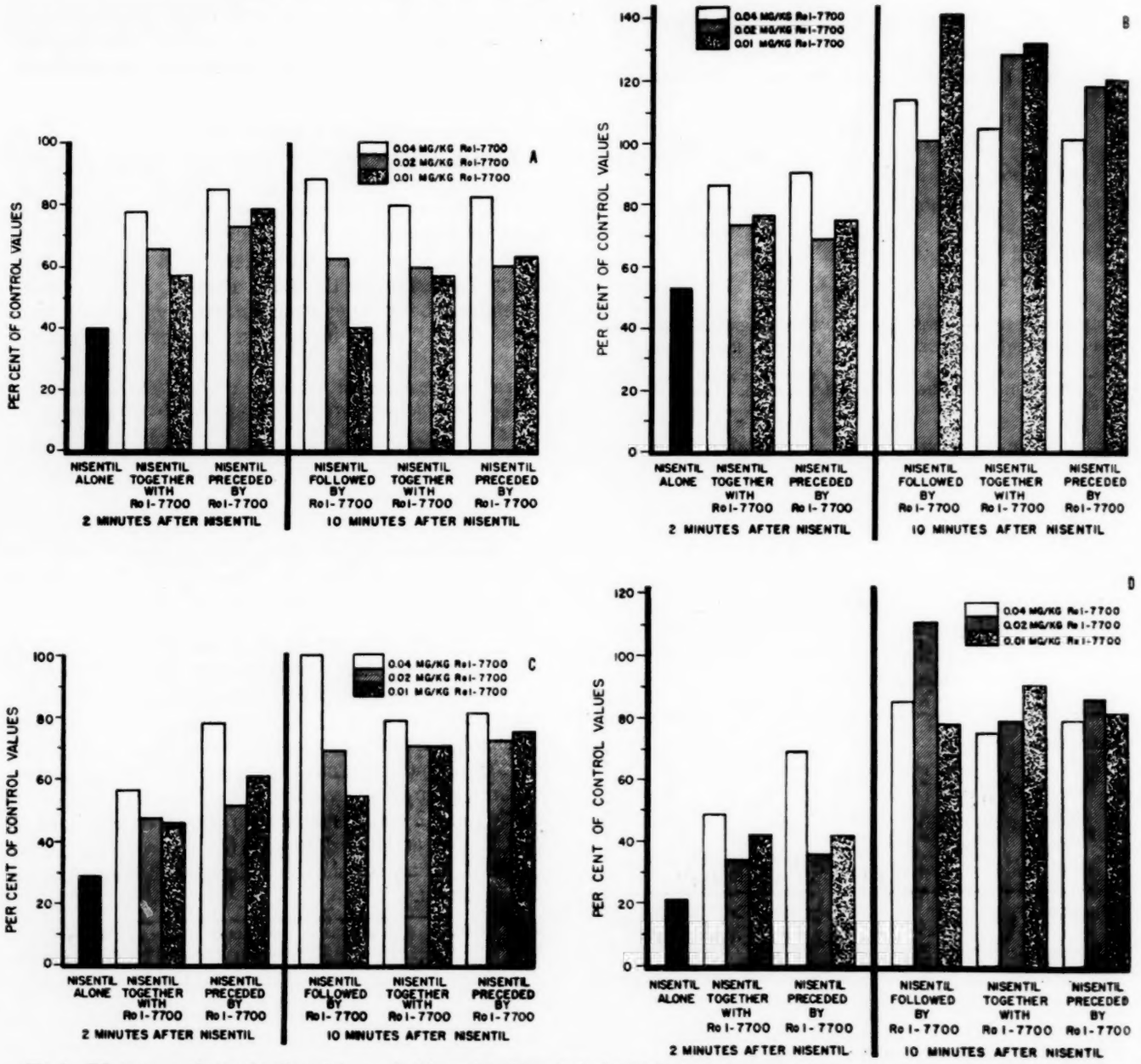

Fig. 3.—Effects on respiratory function of 1 mg. of alphaprodine (Nisentil) hydrochloride per kilogram of body weight alone and combined with levallorphan (Ro 1-7700) at three dose levels with the alphaprodine preceding the antagonist by two minutes, given with the antagonist, or given four minutes after the antagonist. Comparison of effects on *A*, respiratory rates; *B*, tidal volumes; *C*, minute volumes; and *D*, alveolar ventilation rates at the times indicated after administration of alphaprodine. Bars labeled "Nisentil Alone" represent average observations for 30 patients. All other bars represent averages for 10 patients.

After it became evident that the anesthesia can be more easily controlled when the two drugs are injected individually, this method was employed routinely in all cases, with the afore-mentioned dose of the antagonist preceding the analgesic by three to six minutes. Thus, in the three subgroups, 202 patients received alphaprodine and levallorphan from a premixed solution and the remaining total of 650 patients were given levallorphan first followed by alphaprodine.

A 4 liter to 1 liter nitrous oxide–oxygen mixture was then administered by face mask in a semiclosed circuit for three to five minutes and an oropharyngeal airway inserted. If the patient resisted the insertion of the airway, 50 to 200 mg. of thiopental was administered as a 2.5% solution in 25 to 50 mg. increments until the airway could be inserted with ease. The amount of thiopental required was between 50 to 100 mg. in the majority of the cases and seldom exceeded 150 mg. Fifty to 200 mg. of thiopental was used in all patients who were to be intubated. In cases in which intubation was indicated but in which prolonged muscular relaxation was not required, endotracheal intubation was carried out after administration of a single 10 to 50 mg. dose of succinylcholine (Anectine) chloride.

mg. doses of alphaprodine were administered two to three minutes apart, until the desired level of anesthesia was obtained. When this could not be accomplished without depression of the respiratory rate below 12 respirations per minute, additional doses of 25 to 50 mg. of thiopental were given two to three minutes apart. When the duration of surgery exceeded two to three hours, or on the rare occasion when the patient's spontaneous respiratory activity was inadequate at termination of anesthesia, one or more additional 0.4 to 0.6 mg. doses of levallorphan were administered.

The administration of additional 5 to 20 mg. doses of alphaprodine was governed by the signs of lightening of anesthesia (voluntary movements, breath holding, irregular breathing, and tachypnea). The average interval

TABLE 2.—*Average Milligram per Minute Thiopental Requirements of 760* Patients Receiving Alphaprodine Plus Levallorphan and 756 Patients Receiving Alphaprodine Alone as Supplement to Nitrous Oxide–Oxygen–Thiopental Sodium Anesthesia*

Duration of Anesthesia, Min.	No Muscle Relaxant		Relaxant for Intubation		Relaxant for Maintenance	
	Alphaprodine Plus Levallorphan (252 Patients)	Alphaprodine Alone (290 Patients)	Alphaprodine Plus Levallorphan (138 Patients)	Alphaprodine Alone (145 Patients)	Alphaprodine Plus Levallorphan (370 Patients)	Alphaprodine Alone (321 Patients)
0- 30	4.2 ± 0.1†	17.3 ± 1.6	.....	.....	.....	.....
31- 45	2.4 ± 0.3	13.4 ± 0.8	.....	.....	.....	.....
46- 60	2.3 ± 0.3	9.8 ± 0.8	5.3 ± 0.2‡	14.4 ± 1.2‡	4.7 ± 0.1‡	12.4 ± 0.9‡
61- 90	2.1 ± 0.2	7.7 ± 0.7	3.7 ± 0.4	8.4 ± 0.4	3.1 ± 0.1	8.0 ± 0.2
91-120	2.6 ± 0.2	5.9 ± 0.4	3.0 ± 0.3	6.1 ± 0.4	2.1 ± 0.1	6.4 ± 0.7
121-150	2.4 ± 0.1	4.5 ± 0.4	2.5 ± 0.1	4.9 ± 0.7	2.0 ± 0.1	5.2 ± 0.4
151-180	1.3 ± 0.3	.....	2.7 ± 0.3	4.1 ± 0.2	2.2 ± 0.2	4.2 ± 0.8
181 and over	1.8 ± 0.3	.....	3.1 ± 0.1	.....	1.4 ± 0.1	3.2 ± 0.3

* The total number of patients receiving alphaprodine plus levallorphan was 852. The 92 patients not requiring thiopental in the group of 344 not receiving a muscle relaxant were eliminated in this table.
† Standard error.
‡ Includes all cases up to 60 min.

TABLE 3.—*Average Milligram per Minute Alphaprodine Requirements of 852 Patients Receiving Alphaprodine Plus Levallorphan and 756 Patients Receiving Alphaprodine Alone as Supplement to Nitrous Oxide–Oxygen–Thiopental Sodium Anesthesia*

Duration of Anesthesia, Min.	No Muscle Relaxant		Relaxant for Intubation		Relaxant for Maintenance	
	Alphaprodine Plus Levallorphan (344 Patients)	Alphaprodine Alone (290 Patients)	Alphaprodine Plus Levallorphan (138 Patients)	Alphaprodine Alone (145 Patients)	Alphaprodine Plus Levallorphan (370 Patients)	Alphaprodine Alone (321 Patients)
0- 30	3.6 ± 0.2*	0.60 ± 0.08	.....	.....	.....	.....
31- 45	2.2 ± 0.1	0.57 ± 0.02	.....	.....	.....	.....
46- 60	1.9 ± 0.2	0.49 ± 0.02	3.0 ± 0.2†	0.53 ± 0.03†	2.6 ± 0.1†	0.53 ± 0.02†
61- 90	1.5 ± 0.1	0.44 ± 0.03	1.8 ± 0.3	0.48 ± 0.02	1.7 ± 0.1	0.43 ± 0.02
91-120	1.3 ± 0.2	0.35 ± 0.01	1.6 ± 0.3	0.45 ± 0.03	1.4 ± 0.1	0.41 ± 0.01
121-150	1.1 ± 0.1	0.29 ± 0.01	1.2 ± 0.1	0.39 ± 0.01	1.4 ± 0.1	0.37 ± 0.02
151-180	0.9 ± 0.3	.....	1.7 ± 0.3	0.35 ± 0.02	1.0 ± 0.2	0.33 ± 0.02
181 and over	0.9 ± 0.3	.....	1.2 ± 0.2	.....	1.0 ± 0.1	0.28 ± 0.01

* Standard error.
† Includes all cases up to 60 min.

If it was necessary to maintain muscular relaxation throughout surgery, a continuous infusion of succinylcholine was initiated before intubation. Hyperventilation was accomplished with 100% oxygen for about 30 seconds before insertion of the endotracheal tube. After insertion of the oropharyngeal airway or the endotracheal tube, the anesthetic circuit was washed out three times with the 4 liter to 1 liter nitrous oxide–oxygen mixture. Thereafter, nitrous oxide–oxygen was administered in a closed circuit according to a previously described technique.[9] With both the nitrous oxide and the oxygen flow meters set to deliver 500 ml. per minute, the patients inhaled an atmosphere that contained 30 ± 5% oxygen and 70 ± 5% nitrous oxide. If the depth of anesthesia was inadequate at the start of surgery, additional 5 to 20 between supplementary doses of alphaprodine ranged from 8 to 20 minutes. Occasionally, supplementary doses had to be given more frequently early in the anesthesia. Usually, the interval between successive alphaprodine doses could be prolonged with increasing duration of anesthesia.

To assure adequate alveolar ventilation, respirations were assisted by manual compression of the breathing bag throughout anesthesia. Whenever apnea developed, either because of central depression caused by alphaprodine or by the inadvertent administration of too much muscle relaxant, controlled respiration was used until the patient resumed spontaneous respiratory activity.

9. Foldes, F. F.; Ceravolo, A. J., and Carpenter, S. L.: The Administration of Nitrous Oxide-Oxygen Anesthesia in Closed Systems, Ann. Surg. **136**: 978-981 (Dec.) 1952.

METHOD OF EVALUATION

The milligram per minute requirements of thiopental and alphaprodine, as well as the percentage of patients who reacted to auditory and tactile stimulation at the end of surgery, were compared in the series studied and in the control series. Since these criteria had been found to be influenced by the duration of anesthesia,[1] this factor was taken into consideration in the analysis of our findings.

TABLE 4.—*Percentage of Patients Reacting to Stimulation Within Five Minutes of Termination of Surgery*

Duration of Anesthesia, Min.	No Muscle Relaxant: Alphaprodine Plus Levallorphan (344 Patients)	No Muscle Relaxant: Alphaprodine Alone (290 Patients)	Relaxant for Intubation: Alphaprodine Plus Levallorphan (138 Patients)	Relaxant for Intubation: Alphaprodine Alone (145 Patients)	Relaxant for Maintenance: Alphaprodine Plus Levallorphan (370 Patients)	Relaxant for Maintenance: Alphaprodine Alone (321 Patients)
0- 30	95	62	..	..	..	..
31- 45	99	67	..	..	..	..
46- 60	96	77	91*	72*	93*	70*
61- 90	98	84	97	87	97	81
91-120	100	87	90	90	93	84
121-150	100	88	90	91	94	85
151-180	100	..	100	91	97	88
181 and over	100	..	100	..	96	89

* Includes all cases up to 60 min.

Careful observations of respiratory rate and depth, pulse rate, and blood pressure were made in all patients. Changes of these measurements were analyzed in the first 500 patients of the present series. The state of consciousness at the end of anesthesia was also evaluated carefully in these patients, after it had become evident from the observations of the first few patients anesthetized with the new technique that they were surprisingly alert. These 500 patients were divided into four groups according to their ability to answer questions, obey simple commands, and react to tactile stimulation and according to their inability to respond.

The incidence of various postoperative complications during the first 48 hours after surgery and during the interval between the end of anesthesia and the time when patients asked for analgesics were compared in 400 patients anesthetized with the technique under study and in 200 patients of the control series.

RESULTS

Of the 344 patients in the alphaprodine–levallorphan series who did not receive a muscle relaxant and in whom no endotracheal intubation was performed, 92 (27%) did not require any thiopental. The data summarized in table 2 show that the average milligram per minute requirements of thiopental were inversely proportional to the duration of anesthesia, both in the alphaprodine–levallorphan and in the control series. It is also evident that the milligram per minute thiopental requirements were considerably less in the series that received alphaprodine and levallorphan than in the series that received alphaprodine alone. In contrast, milligram per minute alphaprodine requirements were considerably higher when alphaprodine and levallorphan instead of alphaprodine alone were used (table 3). In general, the milligram per minute alphaprodine requirements in both series were also inversely proportional to the duration of anesthesia.

Table 4 indicates that the percentage of patients who reacted within five minutes of termination of surgery was somewhat higher in the alphaprodine–levallorphan series than in the control series. This difference in reactivity was greater when the duration of anesthesia was not more than 60 minutes. Of the 344 patients who did not receive a muscle relaxant, 27 (7.9%) developed apnea that lasted 2 to 10 minutes. This usually occurred early during anesthesia if the injection of thiopental followed too closely the administration of a dose of alphaprodine. When sufficient time was allowed for the development of the full effect of alphaprodine and when thiopental was not administered prematurely, this complication was seldom encountered. In the majority of the remaining 317 patients in this subgroup, the unassisted tidal volume was between 300 and 400 ml.

Analysis of the initial and terminal ranges and the initial and terminal averages of respiratory rates, pulse rates, and blood pressure readings for 500 patients of the present series showed no excessive increase or decrease of these measurements. Occasionally, a marked rise of the systolic and a smaller elevation of the diastolic blood pressure were encountered during anesthesia. This hypertension, the mechanism of which will be discussed later, could be easily corrected by the administration of 5 to 10 mg. of hexamethonium (Hexameton) chloride.

Table 5 indicates that in the groups of the alphaprodine–levallorphan series (500 patients), 55% to 72% of the patients whose state of consciousness was evaluated were capable of answering questions, that 78% to 88% obeyed commands or answered questions, that 9% to 17% reacted to tactile stimulation, and that only 2% to 10% did not react to stimulation within five minutes of termination of surgery. The general appearance of the patients was, as a rule, excellent throughout surgery and during the postanesthetic period. The skin was pink and dry, and the capillary tone was excellent. Despite adequate premedication with parasympatholytic agents, marked miosis was frequently encountered.

In only five of the hospitalized and three of the ambulatory patients were nausea and emesis encountered

TABLE 5.—*State of Consciousness, Within Five Minutes of Termination of Surgery, of 500 Patients Receiving Alphaprodine Plus Levallorphan*

	No Muscle Relaxant (200 Patients) %	Relaxant for Intubation (100 Patients) %	Relaxant for Maintenance (200 Patients) %
Answering questions	72	67	55
Obeying commands	16	14	23
Reacting to tactile stimulation	10	9	17
Not responding	2	10	5

immediately on recovery from anesthesia. The nausea in one of the ambulatory patients was sufficiently disturbing to necessitate hospitalization for 24 hours. The incidence of postoperative complications was not strikingly different in the alphaprodine–levallorphan and in the alphaprodine series, as judged by the comparison of 400 patients of the former and 200 patients of the latter series. Generally, nausea and vomiting occurred more frequently in the patients who had received a muscle re-

laxant throughout surgery than in those who did not. This is not surprising, since the former, in contrast to the latter, underwent predominantly intraperitoneal operations.

Analysis of the postoperative analgesic requirements of these 400 and 200 patients, respectively, revealed that in both series approximately 50% of the patients who received a muscle relaxant for intra-abdominal procedures required an anodyne in the first six hours postoperatively, but that less than 30% of the patients who underwent extraperitoneal surgery and did not receive a muscle relaxant required analgesics during this period. Similarly, while an average of 40% of the patients who underwent extraperitoneal surgery did not require analgesics in the first 24 hours postoperatively, an average of less than 15% of the patients for whom intraperitoneal surgery was performed did not need analgesics during this period.

COMMENT

Effects of Dosages.—It is evident from the data presented that a dose of levallorphan of 0.02 mg. per kilogram of body weight given intravenously three to six minutes prior to the intravenous injection of 1 mg. per kilogram of body weight of alphaprodine prevented, to a considerable degree, the respiratory-depressing effects of the latter drug, without interfering noticeably with its analgesic action. Since repeated, subsequent alphaprodine doses of 5 to 20 mg. that were required for maintenance of adequate anesthesia did not cause respiratory depression in the majority of patients, and since additional doses of levallorphan were needed only in a small number of patients, it is safe to assume that the effect of the antagonist lasts for two to five hours. The simultaneous use of a short-acting analgesic, such as alphaprodine, with a comparatively long-acting narcotic antagonist would be expected to prevent postanesthetic respiratory depression. Indeed, it was shown that this complication was encountered in only 4 of the 400 patients who received alphaprodine and levallorphan and for whom postoperative complications were analyzed. While the initial levallorphan–alphaprodine ratio was 1 to 50, the ratios of the total doses of these two agents were higher and varied, ranging between 1 to 60 and 1 to 120, depending on the total dose of alphaprodine and the duration of anesthesia.

Sensitivity of Patients.—As is true of most analgesics and hypnotics, the sensitivity to alphaprodine varied considerably in different individuals. Patients who required large doses of alphaprodine usually were also resistant to its effects on respiration so that, with this technique, very large doses (as much as 780 mg. in 165 minutes) could be administered without any ill-effects during or after anesthesia. It was also noted that the effectiveness of levallorphan in preventing respiratory depression induced by alphaprodine varied to some extent. On occasion, especially in the aged patient, the initial dose of alphaprodine caused marked respiratory depression, in spite of the administration of levallorphan. Apnea, however, was encountered only if the time interval between the administration of levallorphan and the initial dose of alphaprodine was too short, or if a dose of thiopental followed an injection of alphaprodine too closely. Apnea, which ranged in duration from 2 to 10 minutes, did not tend to return after subsequent fractional doses of alphaprodine. In the majority of patients, however, there was no undue depression of the respiratory rate and the respiratory tidal volume was satisfactory unless depressed by the simultaneous use of succinylcholine in patients who required muscular relaxation.

Patients exhibited unusual sensitivity to the effects of thiopental on respiration after the administration of the relatively large doses of alphaprodine used in this study. Not infrequently the injection of 50 to 100 mg. thiopental caused marked, although transient, respiratory depression that was not counteracted by levallorphan. Fortunately, however, thiopental showed an even greater potentiating effect on the hypnotic and analgesic actions of alphaprodine. Although it was possible to induce adequate anesthesia with nitrous oxide–oxygen after the administration of levallorphan and alphaprodine without thiopental in 27% of the patients who underwent extraperitoneal surgery, the administration of 50 to 200 mg. of thiopental was necessary to obtain satisfactory operating conditions without excessive doses of alphaprodine in the remaining 73%.

Dosage Requirements.—The observation that the average milligram per minute requirements of thiopental and alphaprodine were inversely proportional to the duration of anesthesia is in agreement with previous experiences when meperidine or alphaprodine were used without levallorphan for supplementation of nitrous oxide–oxygen–thiopental anesthesia.[1] Also, depending on the length of anesthesia, the milligram per minute alphaprodine requirements were three to six times greater (table 3) and the thiopental requirements two to five times smaller (table 2) in the alphaprodine–levallorphan series than in the alphaprodine series. The differences in the requirements of thiopental and of alphaprodine in the corresponding groups of the series presented in this study and of the control series are statistically significant ($p < 0.001$). The decrease in the milligram per minute requirements of alphaprodine with increasing duration of anesthesia indicates that repeated doses, in spite of this analgesic's short duration of effect, have a cumulative effect. This cumulative effect of alphaprodine, however, is less marked than that of meperidine.[1]

Individual Complications and Reactions.—Approximately 5% of the patients, anesthetized with the method described, showed significant circulatory changes not related to the operative course. In these patients, marked elevation of blood pressure was encountered despite good alveolar ventilation and adequate depth of anesthesia. This complication usually occurred in patients with pathological conditions related to the hyperirritability of the autonomic nervous system, such as hypertension, hyperthyroidism, and duodenal ulcer, on whom upper abdominal operations, involving traction on the stomach, duodenum, or gallbladder, were performed. The incidence of hypertension did not differ in this series of patients from that observed in other patients anesthetized with similar methods. Blood pressure could invariably be restored to and kept at the preanesthetic levels by the intravenous administration of one or more 5 mg. doses of hexamethonium.

Postoperative Recovery.—The percentage of patients who reacted to stimulation at termination of surgery was greater in the alphaprodine–levallorphan series than in the control series. This quantitative difference, however, was overshadowed by the pronounced qualitative difference in the state of consciousness observed between the patients of the two series. One-half to two-thirds of the patients in the groups receiving alphaprodine and levallorphan were capable of answering questions intelligently within two to five minutes after discontinuation of the administration of nitrous oxide–oxygen. Many of the patients showed spontaneous interest in their surroundings and inquired about the outcome of the operation. Nevertheless, they were well sedated and did not complain of pain. Excitement on emergence from anesthesia was only infrequently encountered, usually in patients with a history of chronic excessive alcohol consumption.

Because of the rapid postanesthetic recovery of consciousness, the method of anesthesia described is also suitable for the performance of various minor surgical procedures in ambulatory patients. As a rule, such patients accompanied by a responsible adult were capable of leaving the hospital within one to two hours after termination of surgery. In only a few instances was it necessary, because of nausea, to keep the patient for a longer period in the recovery room. The incidence of nausea was found to be decreased when the patients received 100% oxygen for two to three minutes after discontinuation of the nitrous oxide–oxygen anesthesia.

Observation of postoperative complications and analgesic requirements revealed no marked differences between the alphaprodine–levallorphan and alphaprodine series. Both the incidence of nausea and emesis and the need for analgesics were considerably higher in patients who underwent intraperitoneal operations than in those for whom extraperitoneal surgery was performed. The fact that close to 40% of the patients on whom extraperitoneal operations were performed did not ask for analgesics in the first 24 hours should serve as a reminder against the routine postoperative administration of analgesics.

Evaluation of Technique.—Whenever a new drug or a new technique is introduced, its advantages and disadvantages should be carefully weighed and its indications critically evaluated. It is often difficult to appraise the merits of a new clinical procedure objectively. The mere fact that a method is under study usually means that it is applied by the more experienced staff members. The "man behind the method" is and always will be an important factor in the success or failure of a given technique. In all fairness, it must be pointed out that the method described requires a thorough understanding of respiratory physiology and of the pharmacology of the various drugs used. The technique belongs, at least for the present, in the hands of the experienced anesthesiologist and is not recommended for the novice or for those who lack the necessary physiological and pharmacological background. The greater the number of drugs used, the greater the hazards of their management.[10] When properly applied, however, this technique will cause little or no interference with the homeostatic mechanisms of the patient during and after surgery. In addition, this technique will make possible a rapid postanesthetic recovery of consciousness.

The question whether the use of relatively large doses of an analgesic preceded by a narcotic antagonist, in combination with small doses of thiopental, is preferable to the use of small doses of that analgesic in combination with large doses of that barbiturate can be answered only after more extensive investigations are made by other workers. In this respect, it is encouraging that results similar to ours have been obtained with the combined use of alphaprodine and levallorphan by others.[11] On the basis of experience reported to date, it can be stated that alphaprodine, because of its short duration of action and relative freedom from side-effects, is eminently suitable for supplementation of nitrous oxide–oxygen–thiopental anesthesia. It is also certain that levallorphan, in doses that by themselves have insignificant effects on respiration,[2] is capable of antagonizing the respiratory effects of large doses of alphaprodine and other potent analgesics.[12] Levallorphan should, therefore, be readily available to anesthesiologists who use potent analgesics for supplementation of nitrous oxide–oxygen anesthesia.

SUMMARY AND CONCLUSIONS

In a new technique the short-acting analgesic alphaprodine (Nisentil) hydrochloride was used in combination with the narcotic antagonist levallorphan (Lorfan) tartrate (*l*-3-hydroxy-N-allylmorphinan) for supplementation of nitrous oxide–oxygen–thiopental (Pentothal) sodium anesthesia. The results in 852 patients managed with the new technique were compared to those in 756 patients in whom nitrous oxide–oxygen–thiopental anesthesia was supplemented by alphaprodine alone.

The milligram per minute requirements of thiopental were significantly decreased and the milligram per minute requirements of alphaprodine significantly increased in the series of patients who received alphaprodine and levallorphan, as compared to the patients of the control series. In 92 (27%) of 344 patients on whom extraperitoneal surgery was performed, satisfactory operating conditions could be obtained by alphaprodine and levallorphan without the use of thiopental. In both series the milligram per minute thiopental and alphaprodine requirements were inversely proportional to the duration of anesthesia. The percentage of patients who reacted to stimulation at termination of surgery was somewhat higher in the alphaprodine–levallorphan series than in the control series. Moreover, the state of consciousness of the patients in the former series was far superior to that of the patients in the control series. Excellent operating conditions could be maintained with the technique described for both major and minor surgical procedures. Levallorphan antagonized the respiratory depressing effects of alphaprodine to a considerable degree without causing any apparent diminution of analgesic activity.

10. Foldes, F. F., and Swerdlow, M.: The Use and Abuse of Anesthetic Drugs, Pennsylvania M. J. **57**: 1160-1167 (Dec.) 1954.
11. Stoelting, V. K.: Personal communication to the authors. Agnone, E. J.: Personal communication to the authors. Kepes, E. R.: Personal communication to the authors.
12. Footnote 8*a*, *b*, and *c*.

No major postanesthetic complications were encountered. The incidence of minor postoperative complications was not markedly different in the series of patients who received alphaprodine and levallorphan, as compared to the series that was given the analgesic alone. The postanesthetic analgesic requirements were about the same in the series under study and the control series. Approximately 40% of the patients who underwent extraperitoneal surgery did not require analgesics in the first 24 hours. The encouraging results obtained with the new technique warrant further studies of the use of alphaprodine and levallorphan for supplementation of nitrous oxide–oxygen anesthesia.

Pride and Locust streets (19) (Dr. Foldes).

CONTROLLED ANALGESIA WITH CONTINUOUS DRIP MEPERIDINE

ANALYSIS OF ONE THOUSAND CASES

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and
Charles R. Stephen, M.D., Durham, N. C.

• ***Meperidine was administered intravenously by continuous drip in a series of surgical patients as an adjunct to anesthesia with thiopental sodium, nitrous oxide, and oxygen. The results were compared with those from a group anesthetized with thiopental sodium, nitrous oxide, and oxygen but without the meperidine.***

The meperidine was found to reduce by 51% the amount of thiopental sodium required per hour. The continuous drip method is reported to give a smoother anesthesia, with less danger of severe respiratory depression and hypotension, than is obtained by single injections of meperidine.

For several years anesthesiologists have used intermittent doses of meperidine intravenously to reinforce the analgesia during thiopental (Pentothal) sodium–nitrous oxide–oxygen anesthesia. Neff and co-workers [1] described first in 1947 the use of meperidine in small repeated doses intravenously as an adjunct to general anesthesia. Since that time many workers [2] have reported the value of intermittent isolated administrations of this drug, but there are only a few writers [3] who have reported the use of a continuous intravenous infusion of a weak solution as an aid to analgesia. Randall and his co-workers [3b] found certain advantages in a continuous dilute infusion of the drug. Garcia, Waltman, and Lubin [4] employed a continuous infusion in 2,500 patients to provide analgesia during the first stage of labor. This group pointed out the presence of analgesia without marked associated hypnosis.

Armed with experience gained by the use of succinylcholine as a continuous dilute infusion, we felt that what could be done for muscular relaxation might be accomplished to some degree for analgesia. Perhaps a more controllable analgesic effect would result from a continuous intravenous administration of a dilute meperidine hydrochloride solution, without the occasional severe respiratory depression and hypotension which can occur [5] immediately after a single dose of 15 to 50 mg. intravenously. Meperidine is primarily analgesic and only mildly hypnotic in action. It has been used so widely as a narcotic agent that its pharmacological properties will not be reviewed. It has been ascertained that the compound is extremely stable, both in concentrated and in dilute solutions.[6]

METHOD OF STUDY

One thousand anesthetic administrations are reported in this preliminary series. In 800 the anesthesia was thiopental sodium, nitrous oxide–oxygen, and meperidine drip, and in 200, serving as a control series, the anesthesia was thiopental sodium and nitrous oxide–oxygen only. In all patients thiopental sodium in a 2 or 2.5% solution was used for induction and was employed intermittently during maintenance. Nitrous oxide–oxygen in a 75:25 ratio was given by semiclosed circle absorption or nonrebreathing techniques, and meperidine hydrochloride (0.5 mg. per milliliter in 5% dextrose in water) was dripped continually or intermittently by vein as required throughout the procedure. Usually the analgesic drug was allowed to flow rapidly for several minutes during induction until the respiratory rate began to slow; then it was regulated according to the

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Read in the Symposium on New Agents and Methods for Analgesia and Anesthesia before the Section on Anesthesiology at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 8, 1955.

1. Neff, W.; Mayer, E. C., and de la Luz Perales, M.: Nitrous Oxide and Oxygen Anesthesia with Curare Relaxation, California Med. **66**: 67-69 (Feb.) 1947.

2. Brotman, M., and Cullen, S. C.: Supplementation with Demerol During Nitrous Oxide Anesthesia, Anesthesiology **10**: 696-705 (Nov.) 1949. Hofmann, A.: Die intravenöse Dolantin-Evipan-Na-Narkose, Chirurg. **21**: 65-68 (Feb.) 1950. Harris, A. J.: Management of Anesthesia for Congenital Heart Operations in Children, Anesthesiology **11**: 328-332 (May) 1950. Ruddell, J. S.: Flaxedil as Adjuvant in General Anaesthesia Particularly with Nitrous Oxide and Intravenous Pethidine, Lancet **1**: 953-954 (May 20) 1950. Mushin, W. W., and Rendell-Baker, L.: Pethidine as Supplement to Nitrous Oxide Anaesthesia, Brit. M. J. **2**: 472 (Aug. 27) 1949. Griffiths, H. F.: Pethidine as Adjunct to Nitrous Oxide and Oxygen Anaesthesia, ibid. **2**: 763-764 (Sept. 30) 1950. Fenster, M. N.: Nitrous Oxide as Inhalation Anesthetic, J. M. Soc. New Jersey **48**: 281 (June) 1951. Pearce, C.: Intravenous Pethidine in Anaesthesia (Report on 330 Cases), Brit. J. Anaesth. **23**: 205-213 (Oct.) 1951. Ballantine, R. I. W.: Anaesthesia for Thoracoplasty, Anaesthesia **7**: 19-23 (Jan.) 1952. Auld, W.: Pethidine, Curare, Nitrous Oxide-Oxygen Anaesthesia in Children, ibid. **7**: 161-165 (July) 1952.

3. (*a*) Johnson, P. D.: Pethidine as Adjuvant to Nitrous Oxide and Oxygen Anaesthesia, Brit. M. J. **2**: 705-707 (Sept. 22) 1951. (*b*) Randall, H. S.; Belton, M. K., and Leigh, M. D.: Continuous Infusion of Demerol During Anaesthesia, Canad. M. A. J. **67**: 311-313 (Oct.) 1952. (*c*) Jeffcoate, T. N. A.; Baker, K., and Martin, R. H.: Inefficient Uterine Action, Surg., Gynec. & Obst. **95**: 257-273 (Sept.) 1952. (*d*) Footnote 1.

4. Garcia, C. R.; Waltman, R., and Lubin, S.: Continuous Intravenous Infusion of Demerol in Labor, Am. J. Obst. & Gynec. **66**: 312-318 (Aug.) 1953.

5. Bodman, R. I.: The Depression of Respiration by the Opiates and Its Antagonism by Nalorphine, Proc. Roy. Soc. Med. **46**: 923-930 (Nov.) 1953.

6. Winthrop-Stearns: Personal communication to the authors.

respiratory rate of the patient and his analgesic requirements. Correct administration of this drug depended on the anesthesiologist's knowledge, gained by experience, of the most painful parts of surgical procedures. Topical anesthetic drugs were employed when it was believed that laryngeal and tracheal reflexes might be troublesome

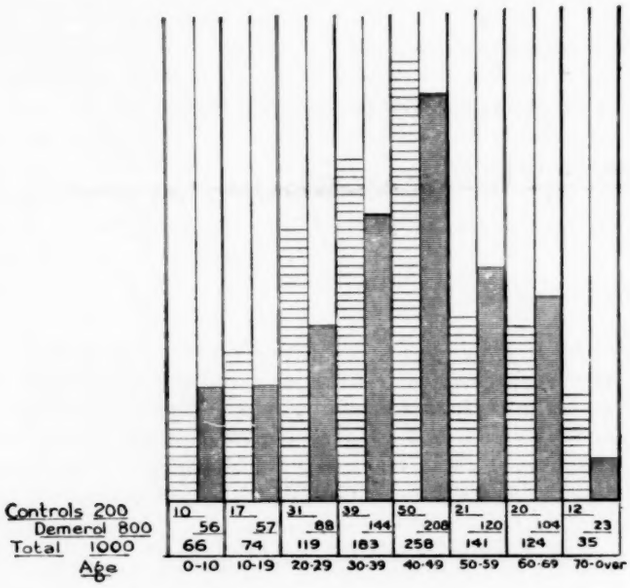

Fig. 1.—Age distribution of patients included in study.

during the operative procedure. Muscle relaxant drugs were used to facilitate endotracheal intubation and in those operations where relaxation was required.

The principal types of operation for which this technique was chosen were plastic, orthopedic, and other extra-abdominal procedures not requiring deep anesthesia. However, this technique has been employed successfully, in conjunction with muscle relaxant drugs, for intra-abdominal and intrathoracic operations where the cautery was being employed.

It is believed that the use of a specific analgesic such as meperidine, in conjunction with other drugs as outlined, would be a sound approach to surgical anesthesia if it could be shown that such combinations, used over a period of several hours, did not cause gross physiological imbalance.[5] With this object in mind, external and internal respiratory function studies are being investigated in some patients receiving this type of anesthesia. In addition, records are being studied carefully to evaluate by clinical means any gross interference with cardiac function.

PREMEDICATION

The preparation of these patients with preanesthetic medication did not differ from the usual. Each patient received morphine sulfate (8 to 15 mg.) or meperidine hydrochloride (50 to 100 mg.) in appropriate dosage with atropine, scopolamine (Hyoscine), or oxyphenonium (Antrenyl) (0.4 to 0.7 mg.) before surgery. In the very nervous or apprehensive patient a short-acting barbiturate such as secobarbital (Seconal) or pentobarbital (Nembutal) in dosage of 50 to 100 mg. was given the evening before operation and two hours before surgery the morning of operation.

ANALYSIS OF ANESTHETICS

The patients were unselected, and so age groups fell into the distribution shown in figure 1. Smaller amounts of meperidine, as well as of thiopental and nitrous oxide, were required in the older groups, but the recovery time in these was no longer than in younger ages. It was observed that confusion on recovery was considerably less and early mental alertness in the senescent more frequent when meperidine was used in addition to thiopental and nitrous oxide. In addition to the 1,000 patients herein reported, meperidine drip was effectively used as an analgesic agent in 76 cases of spinal or regional anesthesia in which the operative procedure outlasted the anesthesia. It was used in 50 patients as the sole agent for minor procedures such as burn dressings and was found to be satisfactory in cases in which very much analgesia was not required.

Figure 2 shows that, in the total patients operated on, the thiopental required was 675 mg. per hour in those receiving thiopental sodium and nitrous oxide as the sole anesthesia, whereas only 350 mg. of thiopental sodium per hour was required by the experimental group, in which meperidine drip was used to reinforce the analgesia. This amounted to a 48.1% less thiopental requirement in the meperidine group.

Figure 3 deals with those patients whose operative procedures exceeded four hours and shows 350 mg. of thiopental given per hour in the controls as against 247 mg. per hour in the experimental group, or a decrease in thiopental requirement of 29.4%. This bears out our

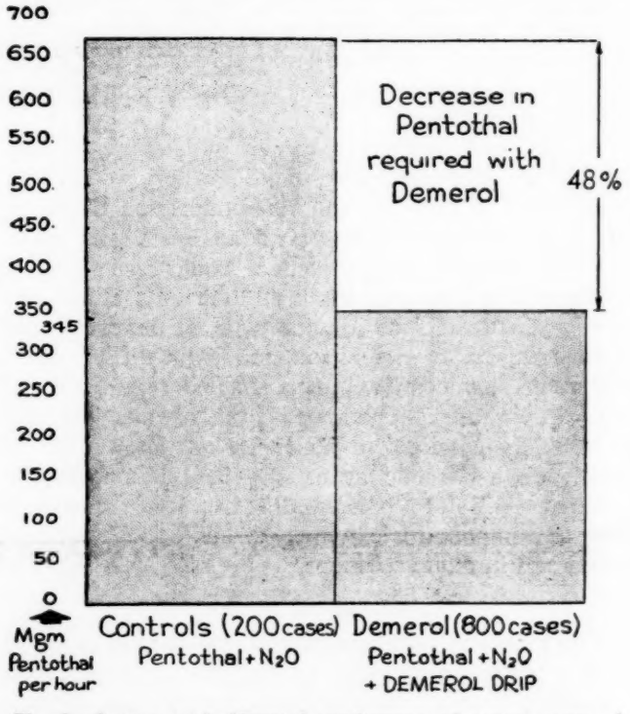

Fig. 2.—Average total thiopental requirements of control group of patients and group receiving meperidine.

understanding of the cumulative effect of the barbiturates. It was observed that in these long cases the recovery time of those having received meperidine drip was much quicker and associated with less confusion and disorientation than in the control group. The explanation of this is obvious, for with a small total amount of thiopental

we would expect rapid recovery, provided meperidine itself did not prolong recovery time. It has been found that meperidine, when used in the continuous drip technique, has a relatively transient effect.

Figure 4 compares patients undergoing plastic procedures (consisting of minor surgery such as skin graft and major surgery such as radical neck dissection) with regard to the thiopental requirement with and without meperidine supplement. These are operations in which analgesia usually is the predominant requirement. It is not surprising to find that 596 mg. per hour of thiopental sodium was required in the controls, in comparison with 380 mg. per hour in those receiving meperidine drip. The combination of thiopental sodium and nitrous oxide–oxygen can provide adequate anesthesia, but only at the expense of injecting into the patient large amounts of a drug that is primarily hypnotic in function. The reinforcement of the barbiturate–nitrous oxide–oxygen combination by meperidine drip seems logical and appears to be effective, since it reduced the total dose of thiopental required by 36.2%.

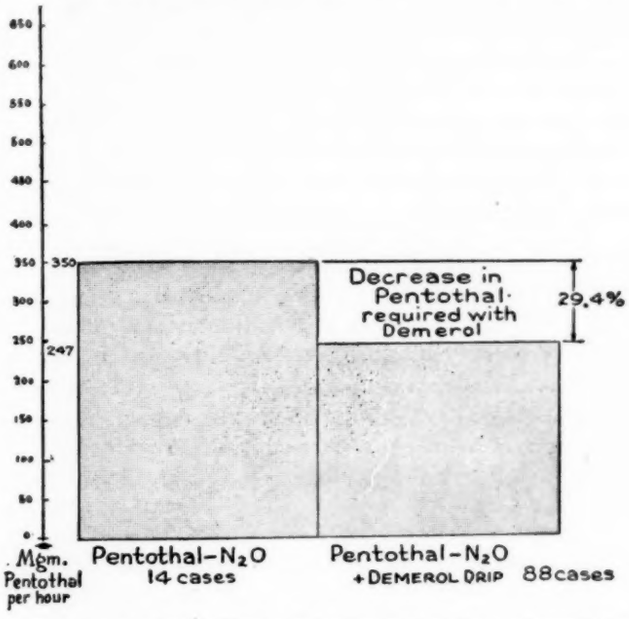

Fig. 3.—Average total thiopental requirements of control and meperidine groups of patients in whom operating time exceeded four hours.

As more experience has been gained with this technique the requirements of the patient for thiopental sodium have become less. Normally with thiopental–nitrous oxide–oxygen anesthesia the maximum analgesia is not present early because adequate time for elimination of nitrogen and its replacement by nitrous oxide has not elapsed by the time the skin incision is made. For this reason meperidine is run in rapidly sometime before the anesthesia by nitrous oxide and thiopental is begun. In this way analgesia is provided by meperidine until nitrous oxide can exert its full action. The total effect is to reduce dependence on thiopental for analgesia and therefore to reduce its requirement.

In arriving at a reflex response that would be a standard measure of wakefulness, it was decided to use the ability of a patient to respond by giving his own name on request or to help himself off the operating table onto the stretcher or bed. Sixty-six per cent of the experimental series were able to respond as indicated at the conclusion of the anesthesia, compared with 43% of the controls.

We found that an average of 72.3 mg. of meperidine per hour was required as reinforcement to the analgesia provided by nitrous oxide. The rate of flow was regulated with the respiratory rate as the principal guide. As the respiratory rate slowed toward 10 per minute the rate of the meperidine drip was decreased. The respiratory rate was not allowed to go below 10 per minute, and at rates below 12 per minute respiration was assisted in most patients in order to ensure adequate ventilation.

Tracheal sensitivity as manifested by "bucking" on the endotracheal tube was found in the control series to be 13% as compared with 2.5% in the experimental group. It should be mentioned that in about one-half of the plastic series transtracheal or other topical anesthesia was performed; so a true picture of the effect of meperidine in depressing the pharyngeal, laryngeal, and tracheal reflexes cannot be obtained from this study. In some patients nothing seemed to prevent bucking on the tube, especially when the head was turned. (It was the clinical impression, however, that there was less bucking when meperidine drip was used than when it was not.) Ruben and Andreassen [7] noted the effect of meperidine on the larynx during the intubation and stated that "Demerol almost obtunded pharyngeal and laryngeal reflexes without deep planes of anesthesia and without hurrying intubation."

There was an insignificant difference between the two groups in the length of time after completion of operation when narcotics for postoperative pain were required. This lends support to the belief that the analgesia provided by meperidine is transient.

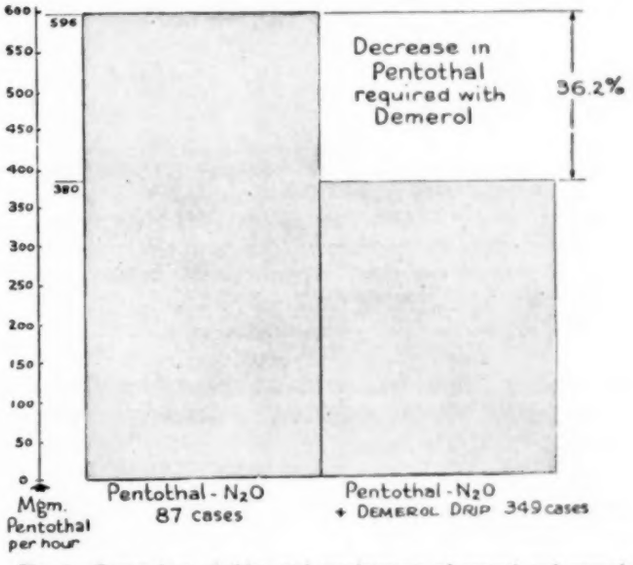

Fig. 4.—Comparison of thiopental requirements of control and meperidine groups of patients undergoing plastic procedures.

ASSOCIATED INVESTIGATIVE STUDIES

In order to determine the effect of this anesthetic combination on external respiration and oxygen utilization, 10 patients have been selected to date in whom

7. Ruben, H., and Andreassen, A. K.: Pharmacological Effects of Pethidine on Larynx Seen During Intubation, Brit. J. Anaesth. **23**: 33-38 (Jan.) 1951.

measurements were made, with use of a McKesson Metabolar, of tidal volume, respiratory rate, minute volume, and oxygen consumption. The table illustrates the type of results which were obtained. It has been noted that tidal volume is not diminished, as a rule, and so the reduction in minute volume is believed to be dependent almost entirely on the reduction in respiratory rate. Of particular interest is the reduction in oxygen utilization seen in these patients. One can speculate that in anesthesia under these conditions a slower respiratory rate is compatible with adequate tissue oxygenation.

A question of particular importance in situations such as this, where the respiratory rate is less than normal, revolves about the possibility of carbon dioxide retention within the patient. In an effort to obtain information regarding this hazard, serial determinations of arterial pH

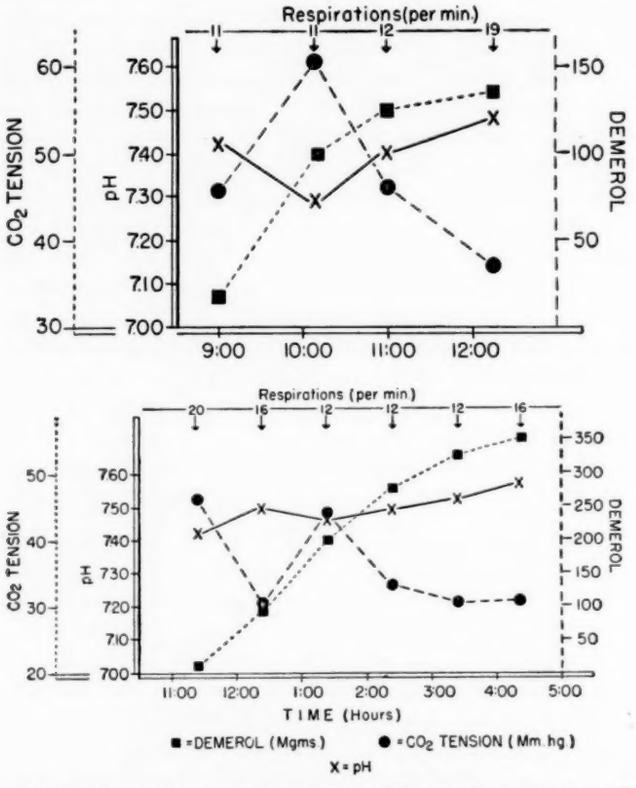

Fig. 5.—Charts of two patients, showing difference in results of serial determinations of arterial pH and carbon dioxide tension during operation. *Above*, carbon dioxide tension increased and pH values decreased. *Below*, pH values increased and carbon dioxide tension decreased.

and carbon dioxide tension have been performed to date in 30 patients. Blood is collected anaerobically through an indwelling Cournand needle in oiled heparinized syringes which are kept in ice until measurements are made, within one to two hours. The pH is measured on the standard Beckman pH meter, and carbon dioxide tensions are determined from the Van Slyke measurements of carbon dioxide content. In a few patients direct arterial oxygen saturation has been measured with the Wood oximeter.

Figure 5 shows two examples of the results that are being obtained. In 7 of these 30 patients there has been noted an increase in carbon dioxide tension and decrease in pH values during operation. In the remaining patients values have been within normal limits. It is our feeling that, barring respiratory obstruction, slowing of spontaneous respirations to 12 per minute can be allowed with this technique of anesthesia without production of carbon dioxide retention in the arterial blood. Arterial oxygen saturation also will remain normal at these rates. Further work is in progress to substantiate these impressions.

An explanation as to why carbon dioxide retention does not occur with the reduced minute volume that may exist with this technique is not obvious. Of course, if oxygen consumption within the patient is reduced then the production of carbon dioxide will in all probability also be less than normal. It is suggested at present that if the respiratory rate falls to 12 or less when this technique is used respirations of the patient should be assisted or controlled.

COMMENT

The basic aim of general anesthesia is to provide satisfactory conditions of hypnosis, analgesia, and muscular relaxation in the patient so that the surgical procedure may be performed with minimal stress and maximum safety both to the patient and to the surgeon. In addition, the anesthesiologist must not be neglected, and the above requisites must be provided within the limitations of his ability and basic pharmacological and physiological

Data on Patient in Whom Cystoscopy Was Done

Time	Meperidine Hydrochloride, Mg.	Thiopental Sodium, Mg.	Tidal Air, Cc.	Respiratory Rate/Min.	Minute Volume, Cc.	Oxygen Consumption, Cc.
10:05	0	0	1,020	7	7,140	505
10:25	50	400	475	11	5,225	425
10:50 (Stimulation)	100	500	690	9	6,210	380
11:10	150	500	660	8	5,280	535
11:45	165	500	610	10	6,100	470
12:10	200	600	710	10	7,100	175

knowledge. If he becomes sufficiently familiar with the present pharmacological array of drugs employed in anesthesia, then he can employ specific drugs for the purposes enumerated above in a safe manner.

Meperidine is a drug that has been shown to produce useful analgesia. When it is used for such a purpose in general anesthesia, certain advantages and disadvantages become apparent. When one considers the relative value of using meperidine in a continuous dilute drip, varying in rate, to produce analgesia, the following points appear to be of importance: On the basis of the reported cases, it is evident that meperidine, administered at an average rate of 72.3 mg. per hour, does definitely enhance analgesia and reduce the total amount of thiopental sodium required in combination with nitrous oxide–oxygen. Smoothness of anesthesia is a somewhat vague clinical term, but in practice most anesthetists realize what is meant by this phrase; the administration of meperidine as a dilute drip will result in fewer variations in vital functions than will larger amounts given intermittently. In surgery today the use of the cautery appears to be becoming more frequent and more necessary; meperidine is a valuable addition to the list of nonexplosive drugs that can be used in anesthesia.

There is evidence to suggest that pharyngeal and laryngeal reflexes are reduced in intensity with the administration of meperidine. Clinical experience as outlined above indicates that meperidine as a continuous di-

lute drip is metabolized rapidly and has a transient analgesic effect. This property allows early awakening of the patient in the postoperative period. Analysis of the anesthesia records of the patients in this series shows minimal interference with cardiac function, as determined by blood pressure, pulse pressure, and pulse rate.

Effect on respiration is of prime importance, because one of the hazards associated with the administration of meperidine is the potential depression of the respiratory center. As indicated above, an effort is being made to find out what degree of respiratory depression may be compatible with normal oxygenation and carbon dioxide tension in the arterial blood. Marked slowing or cessation of respiration was seen seldom in the series reported because of the administration of dilute solution. The continuous drip technique tends to maintain the respiratory center functionally intact, although it causes a gradual slowing of the rate per minute. In emergency situations, when the respiratory rate slows unduly, the administration of nalorphine (n-allylnormorphine) hydrochloride, 5 to 10 mg., intravenously and/or intramuscularly, has provided a rapid reversal of the respiratory depression.

The primary sign of overdosage with this drug is cessation of respiration. If adequate oxygenation is assured by artificial means, cardiac function will not deteriorate at this level of dosage. The possibility of overdosage is lessened by administering this drug as a dilute drip. However, anesthetists using this technique should be able to watch several things at once and should be able to recognize when and how to assist respirations properly.

In 10 of the 800 patients studied urticarial wheals and redness were noted along the course of the vein through which the meperidine was flowing. These allergic reactions disappeared within an hour after the drug was stopped. If the drug was continued, as it was in four patients, the development of further urticarial reactions was prevented by the intravenous injection of tripelennamine, 25 mg. No other specific side-effects were noted in this series.

SUMMARY

In a study of 1,000 patients (200 were control subjects) meperidine hydrochloride in a dilute intravenous drip (0.5 mg. per milliliter) was administered to 800 patients as an analgesic to reinforce the action of thiopental (Pentothal) sodium and nitrous oxide–oxygen for anesthesia. Consideration of the advantages and disadvantages of the employment of meperidine as a continuous dilute intravenous drip suggests that it is a valuable addition to thiopental sodium–nitrous oxide–oxygen anesthesia. Certain investigative work was done in an effort to determine the effect of this technique of anesthesia on tidal volume, minute volume of respiration, oxygen utilization, and alterations in pH and carbon dioxide tension in the arterial blood.

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USE OF CHLORPROMAZINE AND RESERPINE IN THE TREATMENT OF EMOTIONAL DISORDERS

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and
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• Patients receiving uninterrupted medication with either chlorpromazine or reserpine constituted a control group for comparison with a group in whom the medication was interrupted by one month of medication with a placebo. Both chlorpromazine and reserpine caused significant behavioral and affective improvement, especially in the manic phase of manic-depressive psychosis, in agitated states, and in schizophrenic reaction. The drugs differed in their side-effects, but they are valuable to the psychiatrist in controlling destructive, disturbed behavior regardless of the underlying etiology.

In the past two years there have been encouraging reports concerning the use of chlorpromazine [10-(γ-dimethylaminopropyl)-2-chlorophenothiazine hydrochloride] and reserpine (the chief active alkaloid of Rauwolfia serpentina) in the treatment of emotional disorders. Clinical observations thus far have been made mostly on patients in state hospitals.[1]

In general, it has been reported that chlorpromazine and reserpine have a unique calming effect. They have been found to produce a form of sedation without narcosis that causes improvement in the behavior of disturbed, agitated, hyperactive, assaultive, and excited patients, making them more easily manageable. Patients have become quieter, less tense, and more amenable to suggestions from nursing and medical personnel. The need for physical and chemical restraints has been reduced to a minimum. The incidence of accidents and loss or destruction of personal and hospital property has been significantly reduced. The drugs have reduced the need for electroconvulsive treatment, insulin coma treatment, and prefrontal lobotomy in certain patients. Some schizophrenic patients have shown dramatic improvement in their thinking, feeling, and behavior. They have become quieter, less emotionally labile, less concerned about the content of their delusions and hallucinations,

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The reserpine used in this study was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J., under the name Serpasil. The chlorpromazine was supplied by Smith, Kline & French Laboratories, Philadelphia, under the name Thorazine. Deserpidine was supplied by Ciba Pharmaceutical Products, Inc.

and less impulse-ridden in their behavior. Communication of thoughts and feelings to others has improved to such an extent that some of the patients have been more accessible to conventional "interview" type of psychotherapy. Some patients have improved so dramatically that they have been able to leave the hospital after years of confinement. With such consistently favorable reports from various investigators in different parts of the country appearing in the literature, there naturally has followed a wave of hopeful optimism among all individuals vitally interested in the treatment and management of acutely disturbed psychiatric patients.

The purpose of this paper is to present a preliminary report of our clinical experience in treating a group of patients in a 350-bed private psychiatric hospital with chlorpromazine and reserpine. Furthermore, it is the purpose of the present study to determine the ability of each drug to control disturbed ideation, affect (mood), and behavior, to ascertain by the administration of placebo medication whether or not the drugs are responsible for the clinical improvements observed in patients, and to report the incidence of side-reactions and toxic effects of each drug.

TABLE 1.—*Comparison of Patients in Experimental (Placebo) and Control Groups According to Diagnosis*

	Chlorpromazine		Reserpine	
	Placebo	Control	Placebo	Control
Schizophrenic reactions				
Paranoid	15	6	10	11
Catatonic	1	3	0	1
Simple	2	1	0	0
Hebephrenic	1	0	4	0
Acute undifferentiated	2	1	3	5
Chronic undifferentiated	11	7	8	4
Schizoaffective	1	5	0	0
Depressive reactions				
Involutional	2	1	4	4
Psychotic depressed	1	5	2	2
Organic reactions				
Metabolic	0	1	1	1
Senile	8	5	3	3
Other	0	0	1	0
Neurotic reactions	6	6	3	3
Manic-depressive reaction, manic	1	3	5	3
Totals	51	44	44	37

METHOD OF STUDY

Fifty-one patients treated with chlorpromazine and 44 patients treated with reserpine comprised an experimental group in which a one-month's trial of placebo medication was evaluated. Forty-four patients receiving chlorpromazine and 37 patients receiving reserpine served as a control group. The patients in the control group were selected at random to match the patients in the placebo group according to diagnosis. Comparison of patients in the experimental (placebo) and control groups according to diagnosis is shown in table 1. The patients in the placebo and control groups were generally comparable with respect to diagnosis, severity and duration of illness, dose of the drugs administered, and duration of treatment. The main distinction between the two groups of patients was that patients in the control group received their medication without interruption throughout the study, whereas patients in the placebo group had placebo medication introduced at some point during the course of therapy. Only one investigator knew which patients were in each group and when placebo treatment was instituted.

Multiple, independent clinical observations were made by members of a research team who were thoroughly familiar with the pattern of each patient's illness before drug or placebo treatment was instituted. This research team was comprised of each patient's psychotherapist, members of the nursing staff, and members of the departments of educational and occupational therapy. Each patient was seen by his physician on the average of two to three times per week for interviews lasting 30 to 60 minutes. Each week the physician filled out a special report in which he rated the patient's clinical progress according to selected items of the Malamud and Sands Worchester rating scale.[2] Such items as the patient's appearance, motor activity, aggressiveness, socialization, mood, thought content, and thought processes were evaluated. In addition, the physician was asked to write his own progress note with respect to any changes observed in the patient's ideation, affect, and behavior. Also, from the physician's report such information as dosage, rate of administration, and occurrence of toxic effects or side-reactions was obtained. Members of the nursing staff and departments of educational and occupational therapy made daily progress notes on each patient and submitted their reports separately at the end of each week. Furthermore, the patient's behavior was reported daily to the physician by the nurses at morning and evening conferences.

At the end of each week we reviewed all reports and recorded on a summary sheet such information as patient's name, age, and diagnosis; observable changes in ideation, affect, and behavior; blood pressure; pulse rate; hours of sleep; type and amount of sedation; the use of electroconvulsive treatment, insulin coma treatment, cold wet packs, hydrotherapy, or restraints; and any moves that the patients made to different wards or units of the hospital. From the cumulative data on the summary sheet, improvement or lack of improvement was evaluated by us in each of the three spheres of personality-functioning; namely, the spheres of ideation, affect, and behavior. Improvement was rated as: none, slight, moderate, or marked. No patients were included in the study who received medicaments for less than a month. Most patients were administered the drugs regularly during the period from September, 1954, to April, 1955. Adequate doses of the drugs were given according to recommended

1. Lehmann, H. E., and Hanrahan, G. E.: Chlorpromazine: New Inhibiting Agent for Psychomotor Excitement and Manic States, A. M. A. Arch. Neurol. & Psychiat. **71**: 227 (Feb.) 1954. Winkelman, N. W., Jr.: Chlorpromazine in the Treatment of Neuropsychiatric Disorders, J. A. M. A. **155**: 18 (May 1) 1954. Kinross-Wright, V.: Chlorpromazine—a Major Advance in Psychiatric Treatment, Postgrad. Med. **16**: 297 (Oct.) 1954. Elkes, J., and Elkes, C.: Effect of Chlorpromazine on the Behavior of Chronically Overactive Psychotic Patients, Brit. M. J. **2**: 560 (Sept. 4) 1954. Noce, R. H.; Williams, D. B., and Rapaport, W.: Reserpine (Serpasil) in the Management of the Mentally Ill and Mentally Retarded: Preliminary Report, J. A. M. A. **156**: 821 (Oct. 30) 1954. Barsa, J. A., and Kline, N. S.: Treatment of Two Hundred Disturbed Psychotics with Reserpine, ibid. **158**: 110 (May 14) 1955. Kline, N. S., and Stanley, A. M.: Use of Reserpine in a Neuropsychiatric Hospital, Ann. New York Acad. Sc. **61**: 85 (April 15) 1955. Hoffman, J. L., and Konchegul, L.: Clinical and Psychological Observations on Psychiatric Patients Treated with Reserpine: A Preliminary Report, ibid. **61**: 144 (April 15) 1955.

2. Malamud, W., and Sands, S. L.: A Revision of the Psychiatric Rating Scale, Am. J. Psychiat. **104**: 231 (Oct.) 1947.

dosage schedules. The majority of patients treated with reserpine received 2 mg. or more daily; those who received chlorpromazine were administered 200 mg. or more daily. Most of the medication was oral, although extremely disturbed and agitated patients received the medicaments parenterally.

RESULTS

A comparison of clinical results in the experimental (placebo) and control groups is shown in table 2. Among the 44 patients in the chlorpromazine placebo group who showed initial improvement with chlorpromazine, a significant number (68.2%) relapsed when administration of the drug was stopped, as compared to the number relapsing among 36 improved patients in the control group (13.9%). Similarly, the relapse rate for 39 improved patients in the reserpine placebo group was 66.6%, as compared with 20.7% for the 29 improved in the control group. Furthermore, at the conclusion of the placebo experiment, the patients who received the medicament continuously showed a significantly greater percentage of improvement than did those patients whose medication was discontinued because of placebo treatment. For example, 70.5% of the patients in the chlorpromazine control group showed improvement at the end of the study as contrasted to 27.5% in the chlorpromazine placebo group. Similarly, 62.2% of the patients in the reserpine control group showed improvement at the end of the study as compared with 29.5% of the reserpine placebo group.

TABLE 2.—*Comparison of Clinical Results in Experimental (Placebo) and Control Groups*

	Chlorpromazine			Reserpine		
	Placebo	Control	"t"	Placebo	Control	"t"
Total patients	51	44	....	44	37	....
Patients who improved with drug but later relapsed while on either treatment	30	5	....	25	6	....
Placebo patients who improved upon resumption of drug	17	..	....	19	..	....
Placebo patients who did not improve upon resumption of drug	0	..	....	1	..	....
Placebo patients whose drug was discontinued in favor of other treatment	13	..	....	5	..	....
Patients who improved with drug but relapsed before placebo treatment	0	..	....	1	..	....
Patients who maintained improvement throughout therapy	14 (27.5%)	31 (70.5%)	4.89*	13 (29.5%)	23 (62.2%)	3.76*
Patients who did not improve	7	8	....	5	8	....
Patients who showed initial improvement, % of total patients in group	86.3	81.8	....	88.6	78.4	....
Patients who relapsed after initial improvement, % of total improved patients in group	68.2	13.9	4.17†	66.6	20.7	2.05†

* Significant at the 0.001 level of confidence.
† Significant at the 0.05 level of confidence.

Of 30 patients who improved initially with chlorpromazine but then relapsed after placebo treatment, 13 were changed by their physicians to another form of treatment, so that drug therapy was not resumed. Of the other 17 patients, all improved when drug therapy was resumed. Similar results were observed in the 25 patients receiving reserpine as shown in table 2, one not improving upon resumption of drug therapy, while medication was not resumed with 5.

Recurrence of symptoms that followed placebo medication occurred sooner in patients receiving chlorpromazine than in those receiving reserpine. In the chlorpromazine placebo patients, relapses usually occurred within 24 to 48 hours; whereas in patients receiving reserpine, the relapse occurred from three to seven days later. Conversely, control of disturbed behavior was obtained more rapidly with chlorpromazine than with reserpine when the drugs were administered orally. With chlorpromazine the time required was usually from 24 to 48 hours, whereas with reserpine the optimal clinical effect was usually not obtained for at least a week. However, rapid clinical effect was obtained with both drugs when they were administered parenterally in adequate doses (200 mg. to 400 mg. daily for chlorpromazine and 5 mg. to 10 mg. daily for reserpine). When ever rapid drug effect was desired, however, chlorpromazine was usually the drug of choice.

Over-all evaluation of the effect that these medicaments had upon ideation, affect, and behavior was made in a larger group of 106 patients who received chlorpromazine and 103 patients who were treated with reserpine. As seen in table 3 and the figure, the effects of chlorpromazine and reserpine on ideation, affect, and behavior were similar in quality and degree. It was observed, however, that the improvement in affect and behavior was significantly greater than improvement in ideation in the patients studied. For example, table 4 shows that, in the chlorpromazine group, 78% improved behaviorally and 76% improved affectively, as compared with 53% who improved ideationally. Similarly, in the group treated with reserpine, 74% improved behaviorally and 61% improved affectively, whereas only 38% improved ideationally. The improvement seen in these groups of patients was largely in the range of from none to moderate. The number of patients who showed marked improvement was not impressive. For example, behaviorally, in the chlorpromazine group, 22% were not improved, 39% were slightly improved, 28% were moderately improved, and only 11% showed marked improvement. Behaviorally, in the group treated with reserpine, 26% showed no improvement, 43% showed slight improvement, 23% showed moderate improvement, and only 8% showed marked improvement.

Although the number of patients treated in some of the diagnostic categories, as shown in table 3, is too small to permit statistical evaluation of results, it was our general clinical impression that improvement in ideation,

affect, and behavior was most dramatic in those patients who suffered with the manic phase of manic-depressive psychosis. These patients consistently showed uniform improvement in all three spheres of personality functioning. Depressed patients, on the other hand, showed little to no improvement ideationally or affectively. Some patients with agitated depression, however, showed a slight behavioral improvement. Behavior and affect improved in the restless, agitated, and excited patients regardless of the underlying type of personality disturbance. In other words, the agitated behavior that was observed in patients with schizophrenic reactions, organic reactions (particularly chronic brain syndrome associated with senility), and drug withdrawal states was helped by chlorpromazine and reserpine. The neurotic reactions (obsessive-compulsive and anxiety reactions) and the depressive reactions, as previously mentioned, were altered least by these medicaments.

The incidence of side-reactions and toxic effects for each drug is shown in table 5 for 123 patients who received reserpine and 137 patients who received chlorpromazine. Reserpine caused more uncomfortable, subjective side-reactions,* such as nasal stuffiness, epistaxis, excessive flushing, diaphoresis, chilliness, fatigue, weakness, excessive drowsiness, tremulousness, myalgia, ataxia, and diarrhea, than did chlorpromazine.

TABLE 3—*Comparative Effect of Chlorpromazine and Reserpine on Ideation, Affect, and Behavior*

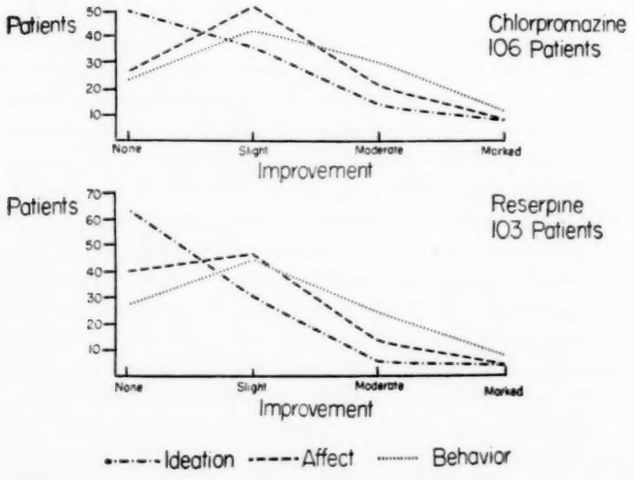
Type of Personality Disorder	No. of Patients	Drug Used *	Ideation				Affect				Behavior			
			NO †	SL	MD	MK	NO	SL	MD	MK	NO	SL	MD	MK
Schizophrenic reactions	51	C	28	18	4	1	15	28	7	1	12	24	12	3
	47	R	31	13	1	2	20	21	4	2	14	18	12	3
Depressive reactions	17	C	10	6	1	0	8	7	2	0	7	6	4	0
	22	R	15	6	1	0	10	11	1	0	8	12	2	0
Organic reactions	16	C	10	5	1	0	2	9	5	0	2	5	7	2
	15	R	10	4	1	0	5	7	3	0	1	9	3	2
Manic-depressive reaction, manic	6	C	0	0	2	4	0	0	2	4	0	0	2	4
	8	R	1	4	2	1	1	2	4	1	1	1	4	2
Neurotic reactions	8	C	2	6	0	0	1	7	0	0	2	6	0	0
	8	R	5	3	0	0	3	5	0	0	3	3	2	0
Alcohol and drug withdrawals	8	C	0	1	5	2	0	1	5	2	0	1	5	2
	3	R	2	0	0	1	1	0	1	1	0	1	1	1
Totals	106	C	50	36	13	7	26	52	21	7	23	42	30	11
	103	R	64	30	5	4	40	46	13	4	27	44	24	8

* C = chlorpromazine, R = reserpine.
† NO = no improvement, SL = slight improvement, MD = moderate improvement, and MK = marked improvement.

TABLE 4.—*Comparison of Improvement in Ideation, Affect, and Behavior in 106 Patients Treated with Chlorpromazine and 105 Patients Treated with Reserpine*

	Chlorpromazine			Reserpine		
	Improved, %	Difference, %	"t"	Improved, %	Difference, %	"t"
Ideation	53	..	.....	38	..	.....
	..	23	3.02 *	..	23	3.38 *
Affect	76	..	.....	61	..	.....
	..	2	0.35 †	..	13	2.03 †
Behavior	78	..	.....	74	..	.....

* Significant at the 0.01 level of confidence.
† Significant at the 0.05 level of confidence.



Effects of chlorpromazine and reserpine on ideation, affect, and behavior of patients.

Bradycardia and hypotension were more frequent in patients treated with reserpine. In contrast, an interesting syndrome of hypertension, hyperthermia, and tachycardia was observed only in patients receiving chlorpromazine. Both drugs caused Parkinsonism, nausea, vomiting, vivid bizarre dreams, pruritus, and a unique form of periorbital, facial, pretibial, and pedal edema. Toxic symptoms of dermatitis and jaundice with or without hepatomegaly were observed only in patients who received chlorpromazine. Thirteen (9.5%) patients taking chlorpromazine developed dermatitis, and 7 patients (5%) developed jaundice. Agranulocytosis did not occur in any patients.

COMMENT

Our results indicate that chlorpromazine and reserpine effectively modify disturbed behavior and affect, although ideation is less dramatically improved. The drugs exert their effect in patients apparently because of their ability

to produce a unique calming and sedative effect without narcosis. The exact site or mode of action of these drugs on the central nervous system is not known. To date, most of the studies made to determine the site or mode of action have utilized reserpine.[3] According to the earlier studies of Bein and others,[3] reserpine acts directly on central autonomic substrates, possibly in the hypothalamus. It was believed that it caused a depression of the central sympathetic functions. Certain clinical phenomena, however, that have been observed in patients receiving these drugs, such as convulsions and Parkinsonism, would seem to indicate that their action might be at a level higher than the hypothalamus. Weiskrantz and Wilson recently reported that the behavior of monkeys with surgical ablation of the amygdaloid nucleus was similar to the behavior observed in monkeys treated with reserpine.[4] These investigators have extended their studies further and have found that a lesion that destroys the cortex of the posterior orbital portion of the frontal lobe and the anteromedial aspect of the temporal lobe, including the amygdaloid nucleus, produces behavior in monkeys that is indistinguishable from that seen in monkeys treated with reserpine.[5] It is known that these portions of the phylogenetically older cerebral cortex do have intimate connections with the hypothalamus and lower centers concerned with the regulation of emotions and behavior.

Because of the rather specific action that these drugs have upon these areas of the brain, they seem to produce an effect similar to that seen in patients with lobotomy. Some have described this effect as a peculiar insulation of the patient against incoming stressful stimuli from the environment. From the psychodynamic standpoint, such an insulating effect is important. Stressful stimuli arising from within or from without the individual usually evoke anxiety, and each individual handles his anxieties according to previously learned ideational and behavioral responses. If the emotionally upset patient can be guarded against incoming stressful stimuli that potentially can further upset the homeostasis of his internal environment, he will be better able to mobilize his previously learned defenses and coping mechanisms in order to handle more efficiently the anxiety or affect evoked by the forces that threaten him from within and from without.

It is unlikely that drug therapy alone could ever totally eliminate all factors of stress that act upon the individual or that drug therapy alone could so alter the individual's responsiveness to stress that anxiety and its physiological concomitants would be forever vanquished. The dynamics and etiology of emotional illness cannot be reduced to such simple terms. However, the advent of these new drugs that seem to have specific regulatory actions on autonomic functions has opened up a whole new field of investigation into the nature, cause, treatment, and management of emotional illness.

The drugs have a relatively wide margin of safety even when used for prolonged periods. Most side-reactions and toxic reactions are reversible and can usually be controlled by temporarily discontinuing use of the drug, by reducing the dose of the drug, or by the use of other medicaments that alleviate the specific symptoms. For example, nasal stuffiness, which is seen so frequently in patients treated with reserpine, is relieved by the use of phenylephrine (Neo-Synephrine) hydrochloride.

Chlorpromazine produces more toxic reactions in patients than does reserpine. Of particular concern to all clinicians is the unusual type of jaundice that has been reported in patients receiving chlorpromazine. The pathogenesis of such jaundice is obscure.[6] There is no definite evidence of hepatocellular damage revealed by clinical laboratory findings or by histological examination. Apparently the bile pools in the canaliculi of the central zones. Laboratory findings are usually those associated with extrahepatic biliary obstruction, that is, elevation in the values for the icteric index and serum bilirubin and alkaline phosphatase. We found that chlorpromazine gave elevated, false-positive values for icteric index determinations. We also observed that a group of patients who received chlorpromazine placebo medication had elevated values for icteric index. It was concluded that the yellow dye in the enteric coating of the chlorpromazine tablet was responsible for the elevation of these values. Accordingly, a modification of the method for determination of the icteric index was devised that corrected adequately the false-positive values and thus made this test a more reliable index of subclinical or impending jaundice in patients receiving chlorpromazine.

TABLE 5.—*Incidence of Side-Reactions and Toxic Reactions*

	Reserpine Patients (Total 123)	Chlorpromazine Patients (Total 137)
Nasal stuffiness	34	2
Epistaxis	3	0
Hypotension	39	20
Hypertension	0	9
Hyperthermia	0	5
Tachycardia	0	12
Bradycardia	21	5
Excessive flushing	11	0
Diaphoresis	2	0
Dizziness	7	7
Chilliness	4	0
Fatigue, weakness	12	3
Syncope	2	1
Blurred vision	0	2
Excessive drowsiness	22	17
Tremulousness	19	1
Myalgia	4	0
Ataxia	7	0
Parkinsonism	2	1
Dry mouth	0	2
Heartburn	0	2
Nausea	7	10
Vomiting	3	7
Diarrhea	9	1
Exacerbation of peptic ulcer	0	1
Edema	9	7
Vivid dreams	3	3
Pruritus	2	2
Dermatitis	0	13
Jaundice	0	7
Hepatomegaly	0	3

3. Bein, H. J.; Gross, F.; Tripod, J., and Meier, R.: Experimentelle Untersuchungen über "Serpasil" (Reserpin), ein neues, sehr wirksames Rauwolfiaalkaloid mit neuartigerzentraler Wirkung, Schweiz. med. Wchnschr. **83**: 1007 (Oct. 17) 1953.

4. Weiskrantz, L., and Wilson, W. A., Jr.: The Effects of Reserpine on Emotional Behavior of Normal and Brain-Operated Monkeys, Ann. New York Acad. Sc. **61**: 36 (April 15) 1955.

5. Weiskrantz, L., and Wilson, W. A.: Personal communication to the authors.

6. Loftus, L. R., and others: Jaundice Caused by Chlorpromazine (Thorazine), J. A. M. A. **157**: 1286 (April 9) 1955. Hodges, H. H., and LaZerte, G. D.: Jaundice and Agranulocytosis with Fatality Following Chlorpromazine Therapy, ibid. **158**: 114 (May 14) 1955.

SUMMARY AND CONCLUSIONS

In the treatment of a group of patients in a private psychiatric hospital, chlorpromazine and reserpine were found to be effective in causing significant behavioral and affective improvement in psychiatric patients. However, in the group of predominantly psychotic patients studied, ideation was less significantly and dramatically improved. Although a significant number of these patients showed improvement behaviorally, the degree of improvement was only slight to moderate. Long-range or lasting improvements in patients receiving these drugs are yet to be evaluated. Chlorpromazine and reserpine are similar in their clinical indications and effectiveness. They may be used interchangeably, although such factors as the incidence of side-reaction and of toxic effects and the rapidity of obtaining clinical effect may influence the choice or preference of one drug to the other in individual cases. Of the two drugs, reserpine is less toxic, but it causes more uncomfortable side-reactions in patients than does chlorpromazine. In most instances, toxic effects or side-reactions can be controlled by merely reducing the dosage. Where rapid drug effect is desired, chlorpromazine is the drug of choice. Chlorpromazine and reserpine are valuable adjuvants to the armamentarium of the practicing psychiatrist, particularly for the control of destructive, disturbed, agitated, and hyperactive behavior, regardless of the underlying etiology. The psychiatric conditions for which these drugs were found to be of clinical use, in descending order, are: (1) manic-depressive psychosis, manic phase; (2) agitated states, particularly those associated with organic brain disease; (3) schizophrenic reaction; (4) depressive reaction; and (5) neurotic reaction.

ADDENDUM

Since the time of writing we have had some experience with the use of Deserpidine, a new alkaloid from Rauwolfia canescens. Deserpidine differs chemically from reserpine in the lack of a methoxy group in ring A. The effect of this new alkaloid was studied with a group of six patients whose response to reserpine had already been well established. There was no observable difference in the effect of Deserpidine as compared with that of reserpine from a clinical standpoint.

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EXPERIMENTAL INVESTIGATIONS ON MECHANISM PRODUCING ACUTE DERMATOPHYTOSIS OF FEET

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• Volunteer subjects exposed themselves by immersing the right foot in a basin of water that had been contaminated either by the previous immersion of a foot with proved fungous disease or by the addition of fungus culture material. Clinical fungous disease of the foot did not result in any of the volunteers, even though the skin was found to have picked up the organisms. There is a sharp distinction between asymptomatic "fungous infection" and clinical "fungous disease" of the feet. Exogenous exposure plays at most a minor role in acute dermatophytosis of the feet.

Other volunteers whose feet carried one type of fungus exposed a foot to water contaminated with a fungus other than that already resident on the skin. In one instance Trichophyton rubrum was thus induced to grow where T. mentagrophytes had existed before. In three instances T. mentagrophytes infection was superposed on the preexistent T. rubrum infection. These four instances in 20 trials with heavily contaminated water did not lead to active attacks of fungous disease.

Public and individual measures for the prevention of fungous disease of the feet should be based on the maintenance of local resistance to infection rather than on measures designed to prevent infection.

For many years public health measures for the prevention of dermatophytosis have been based to a large extent on the assumption that acute attacks of fungous disease of the feet are precipitated principally by exogenous exposure to pathogenic fungi. Among the many objects incriminated have been carpets, bath mats, bathtubs, shoes, slippers, towels, socks, and especially floors of shower rooms and locker rooms and areas around swimming pools. This viewpoint has been supported by statements in the medical literature, although statistical or experimental evidence in favor of it has been conspicuously lacking. The few reports on experimental work that showed that active disease could be produced by inoculation with dermatophytes utilized techniques that did not resemble actually prevailing conditions. The procedures employed were the placing of masses of fungous culture material into macerated toe webs and encasing the inoculated areas by binding with adhesive tape.[1]

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1. von Graffenried, C.: Beitrag zur Frage der mykotischen Dyshidrosis (Kaufmann-Wolf), Dermat. Wchnschr. **66**: 361-371, 1918. Weidman, F. D.: Laboratory Aspects of Epidermophytosis, Arch. Dermat. & Syph. **15**: 415-450 (April) 1927. Peck, S. M.: Epidermophytosis of the Feet and Epidermophytids of the Hands: Clinical, Histologic, Cultural and Experimental Studies, ibid. **22**: 40-76 (July) 1930.

Elsewhere we have reviewed pertinent literature [2] that deals with attempts to demonstrate the presence of pathogenic fungi on the floors of shower rooms and public baths. It suffices here to state that we are aware

of only two isolated instances in which a pathogenic fungus was recovered from a floor on which many presumably fungus-infected subjects had walked.[3] Our own investigations reported elsewhere,[4] however, convince us that many subjects with and some without dermatophytosis must be depositing infected scales almost continuously wherever they tread. In view of this, one may assume that in parts of the world where dermatophytosis is prevalent the feet of most persons are frequently and repeatedly exposed to pathogenic fungi.

The question then arises whether the fungi deposited in the external environment are indeed the cause of acute attacks of fungous disease. There is strong epidemiological and other evidence that speaks against a causal role of exogenous exposure in acute attacks of dermatophytosis, a viewpoint that has been supported by a considerable number of dermatologists.[5] These authors have presented data suggesting that the occurrence of clinically active fungous disease of the feet is principally due to fungi that these persons previously had been carrying on their own feet in a latent, "opportunistic," facultatively pathogenic state. In the presence of lowered resistance of the skin on the feet, these fungi multiply and produce disease. If this theory is correct, and there is much evidence in its favor, exogenous infection would play a minor or negligible role in the causation of acute attacks of dermatophytosis. In fact, 40 years ago pathogenic fungi were found by Schramek [6] to exist in clinically normal skin areas on the feet of patients with clinical fungous disease, and they have often been found on the feet of persons without clinical fungous disease.[4]

Further evidence against the role of exogenous exposure as a cause of fungous disease (as distinguished from asymptomatic fungous infection) was brought by Hopkins and others,[7] who observed that the species of organism causing fungous infections of the feet at a military post occurred in the same ratio in every group examined and that in recurrent attacks of dermatophytosis the organism responsible for the first attack was usually found in subsequent infections. If contagion were an important factor in the spread of the disease, one species of dermatophyte would be expected to predominate in the groups of men who shared the same facilities and different species of fungi would be expected to be the causes of clinical fungous disease in the same subject at various times, in accordance with the individual's exposures to the different species. The experiments described below were undertaken in an attempt to subject to scientific investigation the role of exogenous exposure in the causation of acute attacks of fungous disease of the feet and thus to remove this question from the realm of conjecture. A preliminary report of this work has been made elsewhere.[2]

EXPERIMENTAL EFFORTS TO PRODUCE DERMATOPHYTOSIS

Experiments were conducted to determine an answer to this question: Is foot-bath water contaminated with pathogenic fungi capable of causing acute attacks of dermatophytosis in subjects clinically and mycologically free from this disease?

Technique.—Scrapings of the feet of volunteers were examined twice at weekly intervals for the presence of pathogenic fungi both microscopically in potassium hydroxide preparations and by culture on Sabouraud's medium and in most instances also on cycloheximide (an antibiotic derived from Streptomyces griseus) medium.[8] Sixty-eight subjects whose feet were both microscopically and culturally negative for pathogenic fungi were accepted for participation in these tests. They will hereafter be referred to as "uninfected" volunteers. It must be realized, however, that negative mycologic findings at two weekly examinations are by no means conclusive proof that fungi were not present somewhere on the feet. With 14 of the 68 uninfected volunteers the following technique was employed: A subject with a proved fungous disease of the feet was allowed to immerse both feet for 15 minutes in a sterile basin containing 200 ml. of sterile tap water. Within the subsequent 30 minutes an uninfected volunteer placed his right foot into this presumably contaminated foot-bath water. At the same time the left foot served as a control by being placed in another basin containing 200 ml. of sterile tap water. The feet were allowed to remain in these two basins for 30 minutes. During half of this time the basins were tilted slightly forward to insure complete immersion of the toe webs. The contents of each basin were then centrifuged and the sediments examined by the potassium hydroxide and Hotchkiss-McManus methods. In this manner, it was possible in each instance but two to prove that fungi were actually present in the foot-bath water used to expose the uninfected volunteers.

Due to the difficulties of regularly obtaining the cooperation of persons with active fungous disease of the feet who could serve as a source of fungi to contaminate foot-bath waters, the remaining 54 uninfected volunteers were exposed to foot-bath water to which fungus culture material, prepared by the method of Friedhoff and Rosenthal,[9] had been added. The number of viable fun-

2. Baer, R. L.; Rosenthal, S. A.; Rogachefsky, H., and Litt, J. Z.: Newer Studies on the Epidemiology of Fungous Infections of the Feet, Am. J. Pub. Health **45**: 784-790 (June) 1955.

3. Ajello, L., and Getz, M. E.: Recovery of Dermatophytes from Shoes and Shower Stalls, J. Invest. Dermat. **22**: 17-21, 1954. Gerencser, N.: Epidemiology of Mycosis of Hands and Feet, Orvosi hetil. **81**: 576-578, 1937.

4. Rosenthal, S. A.; Baer, R. L.; Litt, J. Z.; Rogachefsky, H., and Furnari, D.: Studies on the Dissemination of Fungi from the Feet of Subjects With and Without Fungous Disease of the Feet, J. Invest. Dermat., to be published.

5. Williams, C. M.: Tinea of the Nails as a Source of Reinfection in Tinea of the Feet: Preliminary Report, Arch. Dermat. & Syph. **18**: 730-731 (Nov.) 1928. Williams, C. M., and Barthel, E. A.: Tinea of the Toe-Nails as a Source of Reinfection in Tinea of the Feet, J. A. M. A. **93**: 907-910 (Sept. 21) 1929. Modern Treatment of Common Fungous Infections, in Year Book of Dermatology and Syphilology, edited by F. Wise and M. B. Sulzberger, Chicago, Year Book Publishers, Inc., 1937. Sulzberger, M. B.; Baer, R. L., and Hecht, R.: Common Fungous Infections of the Feet and Groins: Negligible Role of Exposure in Causing Attacks, Arch. Dermat. & Syph. **45**: 670-675 (April) 1942. Hopkins, J. G., and others: Treatment and Prevention of Dermatophytosis and Related Conditions, Bull. U. S. Army M. Dept. **77**: 42-53, 1944. Peck, S. M., and Schwartz, L.: Is Dermatophytosis a Significant Occupational Health Problem? Am. J. Pub. Health **35**: 621-624, 1945. Henrici, A. T.: Henrici's Molds, Yeasts, and Actinomycetes: A Handbook for Students of Bacteriology, edited by C. E. Skinner, C. W. Emmons, and H. M. Tsuchiya, ed. 2, New York, John Wiley & Sons, Inc., 1947.

6. Schramek, M.: Befunde bei Pilzerkrankungen der Hände und Füsse, Arch. Dermat. u. Syph. **121**: 630-645, 1916.

7. Hopkins, J. G., and others: Dermatophytosis at an Infantry Post: Incidence and Characteristics of Infection by 3 Species of Fungi, J. Invest. Dermat. **8**: 291-316, 1947.

8. Georg, L. K.: Use of a Cycloheximide Medium for Isolation of Dermatophytes from Clinical Materials, A. M. A. Arch. Dermat & Syph. **67**: 355-361 (April) 1953.

9. Friedhoff, F. W., and Rosenthal, S. A.: A Simple Method for Preparing Homogeneous Suspensions of Dermatophytes and for Estimating the Number of Viable Particles in These Suspensions, J. Invest. Dermat. **23**: 155-162, 1954.

gous particles per 200 ml. of foot-bath water in our tests varied between 670 and 5,600,000, with an average of about 295,000. The 68 uninfected volunteers who participated in these tests were asked not to make any changes in their usual daily hygiene of the feet during the course of the tests. Once a week during the six weeks following exposure to contaminated foot-bath water the volunteers returned for mycologic examination, and every time scrapings from each foot were examined in potassium hydroxide mounts and on Sabouraud's medium and, in most instances, on cycloheximide agar.

Results.—The results obtained in 68 subjects are presented in tables 1 and 2. Filaments were seen in one or more scrapings during the six weeks subsequent to the

TABLE 1.—*Results of Mycologic Examinations of Fourteen Subjects Without Fungous Infection After Exposure to Foot-Bath Water of Persons with Fungous Infection of the Feet*

Volunteer No.	Exposed to	Foot Examined	No. of Weeks After Attempt at Infection													
			1		2		3		4		5		6		7	
			KOH*	C.†	KOH	C.	KOH	C.	KOH	C.	KOH	C.	KOH	C.	KOH	C.
1	T. m.‡	Exposed	—	—	—	—	—	—	—	—	—	—	—	—	..	..
		Control	—	—	—	—	—	—	—	—	—	—	—	—	..	..
2	T. r.§	Exposed	—	—	—	—	—	—	Not done		—	—	Not done		—	—
		Control	—	—	—	—	—	—			—	—			—	—
3	T. m.	Exposed	—	—	—	—	—	—	—	—	—	—	—	—	..	..
		Control	—	—	—	—	—	—	—	—	—	—	—	—	..	..
4	T. r.	Exposed	—	—	—	—	—	—	—	—	+	—	—	—	..	..
		Control	—	—	—	—	—	—	—	—	—	—	—	—	..	..
5	T. r.	Exposed	—	—	—	—	Not done		Not done		—	—	—	—	..	..
		Control	—	—	—	—					—	—	—	—	..	..
6	T. m.	Exposed	—	—	—	—	—	—	—	—	Not done		Not done		..	..
		Control	—	—	—	—	—	—	—	—					..	..
7	T. m.	Exposed	—	—	—	—	—	—	+	—	—	—	—	—	..	..
		Control	—	—	—	—	—	—	+	—	—	—	—	—	..	..
8	T. m.	Exposed	—	—	—	—	Not done		Not done		—	—	+	—	—	T. r.
		Control	—	—	+	—					—	—	—	—	—	—
10	T. m.	Exposed	—	—	—	—	—	—	—	—	—	—	—	—	..	..
		Control	—	—	—	—	—	—	—	—	—	—	—	—	..	..
13	T. m.	Exposed	—	—	—	—	—	—	—	—	—	—	—	—	..	..
		Control	—	—	—	—	—	—	—	—	—	—	—	—	..	..
15	T. m.	Exposed	—	—	—	—	—	—	—	—	—	—	—	—	..	..
		Control	—	—	—	—	—	—	—	—	—	—	—	—	..	..
16	T. m.	Exposed	—	—	—	—	—	—	—	—	—	—	—	—	..	..
		Control	—	—	—	—	—	—	—	—	—	—	—	—	..	..
17	T. m.	Exposed	—	—	—	—	—	—	—	—	—	—	—	—	..	..
		Control	—	—	—	—	—	—	—	—	—	—	—	—	..	..
18	T. m.	Exposed	—	—	—	—	—	—	—	—	—	—	—	—	..	..
		Control	—	—	—	—	—	—	—	—	—	—	—	—	..	..

* Potassium hydroxide mount.
† Culture.
‡ Trichophyton mentagrophytes.
§ T. rubrum.

TABLE 2.—*Results of Mycologic Examinations of Fifty-Four Subjects Without Fungous Infection of Feet After Exposure to Foot-Bath Water Contaminated with Cultures of Dermatophytes*

Volunteer No.	Exposed to	No. of Viable Particles of Dermatophyte in Foot Bath* (200 Ml.)	Foot Examined	No. of Weeks After Attempt at Infection											
				1		2		3		4		5		6	
				KOH†	C.‡	KOH	C.	KOH	C.	KOH	C.	KOH	C.	KOH	C.
20	T. m.§	24,800	Exposed	—	—	+	T. r.	—	—	+	—	—	—	+	—
			Control	—	—	+	—	—	—	+	—	—	—	+	—
22	T. m.	4,320	Exposed	—	—	—	—	—	—	—	—	+	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
23	T. m.	4,320	Exposed	—	—	+	—	—	—	+	—	—	—	—	—
			Control	—	—	—	—	+	—	—	—	—	—	+	—
24	T. m.	15,400	Exposed	—	—	—	—	+	—	+	—	+	—	—	—
			Control	—	—	+	—	+	—	—	—	+	—	—	—
26	T. m.	15,400	Exposed	—	—	—	—	+	—	+	—	—	—	+	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
27	T. m.	36,600	Exposed	—	—	—	—	—	—	—	—	+	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
28	T. m.	26,500	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
29	T. m.	26,500	Exposed	+	—	—	—	+	—	+	—	+	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
32	T. m.	6,800	Exposed	—	—	+	—	—	—	+	—	—	—	—	—
			Control	+	—	—	—	—	—	—	—	—	—	—	—
33	T. r.‖	670	Exposed	—	—	—	—	—	—	+	—	—	—	—	—
			Control	—	—	—	—	+	—	+	—	—	—	—	—
34	T. m.	6,800	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	+	—	+	—	—	—	—	—	—	—	—	—
36	T. m.	43,000	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
42	T. m.	51,200	Exposed	+	—	—	—	+	—	—	—	—	—	—	—
			Control	+	—	—	—	+	—	—	—	+	—	—	—

TABLE 2.—*Results of Mycologic Examinations of Fifty-Four Subjects Without Fungous Infection of Feet After Exposure to Foot-Bath Water Contaminated with Cultures of Dermatophytes*—Continued

Volunteer No.	Exposed to	No. of Viable Particles of Dermatophyte in Foot Bath* (200 Ml.)	Foot Examined	No. of Weeks After Attempt at Infection											
				1		2		3		4		5		6	
				KOH†	C.‡	KOH	C.	KOH	C.	KOH	C.	KOH	C.	KOH	C.
45	T. m.	8,540	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
51	T. m.	5,160	Exposed	—	—	—	—	—	—	—	—	+	—	—	—
			Control	—	—	—	—	—	—	+	—	—	—	—	—
53	T. m.	5,980	Exposed	+	T. m.	—	—	—	—	—	—	—	—	+	—
			Control	—	—	—	—	—	—	—	—	—	T. m.	—	—
57	T. m.	12,600	Exposed	+	—	—	—	+	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
61	T. m.	25,600	Exposed	+	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
63	T. m.	25,600	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
66	T. m.	35,400	Exposed	—	—	—	—	—	—	—	—	—	—	+	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
69	T. m.	48,200	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
70	T. m.	48,200	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
71	T. m.	172,200	Exposed	—	—	+	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
72	T. m.	172,200	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
73	T. m.	172,200	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
76	T. m.	40,000	Exposed	—	—	+	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	+	—	—	—	—	—
77	T. r.	64,200	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
78	T. r.	64,200	Exposed	—	—	—	—	—	—	+	—	—	—	+	—
			Control	—	—	—	—	—	—	—	—	—	—	+	—
80	T. r.	8,460	Exposed	—	—	—	—	—	—	—	—	—	—	+	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
81	T. m.	41,500	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	+	—	+	—	+	—	—	—
82	T. m.	498,000	Exposed	—	—	—	—	—	—	+	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
84	T. m.	498,000	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
86	T. m.	430,000	Exposed	—	—	+	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
87	T. m.	746,000	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
88	T. m.	746,000	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
89	T. m.	67,200	Exposed	+	—	—	—	—	E. f.	—	E. f.	—	—	+	E. f.
			Control	—	—	—	E. f.¶	—	E. f.	—	—	—	—	+	E. f.
90	T. m.	67,200	Exposed	—	—	—	—	+	—	—	—	—	—	—	—
			Control	—	—	—	—	+	—	—	—	—	—	—	—
91	T. m.	30,200	Exposed	+	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
92	T. m.	68,600	Exposed	—	—	+	—	—	—	—	—	+	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
93	T. m.	68,600	Exposed	—	—	+	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
94	T. m.	19,000	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	+	—	—	—	—	—	—	—
95	T. m.	2,600	Exposed	+	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
96	T. m.	10,300	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
97	T. m.	10,300	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
98	T. m.	10,300	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
99	T. m.	35,400	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
100	T. m.	1,740	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
101	T. m.	5,600,000	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	+	—	—	—	—	—
102	T. m.	5,600,000	Exposed	—	—	—	—	—	—	—	—	+	—	—	—
			Control	—	—	—	T. r.	—	T. r.	—	—	—	—	—	—
104	T. m.	72,600	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
105	T. m.	13,600	Exposed	+	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
107	T. m.	13,600	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
108	T. m.	13,600	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—
109	T. m.	82,000	Exposed	—	—	—	—	—	—	—	—	—	—	—	—
			Control	—	—	—	—	—	—	—	—	—	—	—	—

* Calculated from plate counts of original stirred suspensions.
† Potassium hydroxide mount.
‡ Culture.
§ Trichophyton mentagrophytes.
‖ T. rubrum.
¶ Epidermophyton floccosum.

deliberate exposure to contaminated foot-bath water in 37 (54%) of the 68 subjects listed in tables 1 and 2, while 31 (46%) were found to be negative. In 19 of these 68 subjects fungi were seen only on the exposed feet, and in 5 only on the unexposed feet. In 13 of the subjects, fungous filaments were seen on both the exposed and control feet. The total number of positive microscopic findings was 49 for the exposed feet and 29 for the unexposed feet. None of the subjects with or without positive microscopic findings developed evidence of clinical fungous disease on either foot. Cultures of Trichophyton rubrum were isolated from three subjects (no. 8, 20, 102), and of Epidermophyton floccosum from subject no. 89. These four subjects had been exposed to water that had been contaminated with T. mentagrophytes. A culture of T. mentagrophytes was isolated from subject no. 53 after he had been exposed to the same species of fungus.

Comment.—Mycologic data were obtained from 14 subjects exposed to the foot-bath water of patients with fungous disease and 54 exposed to foot baths containing large numbers of fungi from cultures. The first method can be assumed to resemble natural conditions, although in a vastly exaggerated form. The more artificial method of using foot baths containing fungous culture material had its own advantages, namely, that relatively enormous doses of fungi could be added to the foot bath, many thousands of times more than could conceivably be encountered in even the most highly contaminated natural environments. Moreover, the number of viable fungous elements added to the foot-bath water could be assayed by a plate count of the fragmented fungous suspensions.[9]

Of the 14 subjects exposed to foot-bath water from infected persons, only 3, approximately 22%, showed fungous mycelia upon subsequent examination (3 on the exposed foot and 2 on the control foot). Of the 54 subjects exposed to material from cultures of dermatophytes, 34, or approximately 63%, showed fungous filaments upon subsequent examination (29 on the exposed foot and sixteen on the control foot). It is improbable that the difference between these two groups is a chance finding. The explanation that fungi taken from growing cultures may be more infectious is highly unlikely to account for our observations. Rather, it may be assumed that the variation in intensity of exposures encountered under seminatural conditions (foot-bath water from individuals with clinical fungous disease) and under entirely artificial conditions (foot-bath water contaminated with an average of 295,000 fungus elements per 200 ml.) accounts for the differences in our results. Apparently the latter exposure is much more adequate for a "take" of these facultatively pathogenic organisms, but it is important to emphasize that even such overwhelming exposures, under conditions that allowed for some maceration on the feet, were incapable of engendering clinically detectable disease. In not a single instance did one of these subjects in whom microscopic results were positive show clinical evidence of fungous infection. It should be noted also that the heavier exposure led to a higher percentage of positive microscopic findings on the control foot (exposed in the experiment to sterile tap water). The frequent finding of fungi on the control foot suggests the easy transfer of fungous elements from one foot to the other.

It appears probable that the demonstration of fungi on the feet of many of the 68 subjects was in most instances due to our deliberate exposure. It is very likely, however, that some of our positive findings were due to an undetected preexisting infection on the feet of these volunteers. This is suggested by the fact that the species of dermatophyte isolated from the feet of four subjects (no. 8, 20, 89, 102) was different from that to which they had been exposed by us. Probably they had previous latent infections with T. rubrum and E. floccosum, and the exposure to T. mentagrophytes in the foot-bath water did not result in a culturally detectable or clinically active infection with T. mentagrophytes. It may be concluded from this that our method of exposure was adequate to result in the establishment, at least temporarily, of pathogenic fungi on the feet of many of our volunteers. Another piece of evidence that supports the assumption that a mycologically undetected preexisting infection accounted for some of our positive results was found in an additional control series of 13 subjects. These volunteers, after preliminary mycologic examination, immersed one foot in sterile tap water. During the subsequent six weeks, both feet underwent weekly mycologic examinations. Eleven of these 13 subjects failed to show fungi in scrapings from their feet after exposure to sterile tap water. One yielded a culture of T. rubrum and showed mycelia upon microscopic examination, and another yielded a culture of T. mentagrophytes. It appears desirable that in the future a sharp differentiation be made between asymptomatic "fungous infection" and "fungous disease" of the feet (dermatophytosis).

No matter whether the fungi found in 37 of the 68 subjects were picked up in the deliberately infected foot baths or came from an undetected presence of the fungi on clinically normal feet, it is a fact that not a single attack of fungous disease of the feet was evoked during the six-week period following such overwhelming fungous exposures. These data conclusively demonstrate that exogenous exposure plays at most only a very minor role in the development of acute attacks of fungous disease of the feet. Rather, as has been suggested by several dermatologists during the past two decades, it is individual resistance, probably mainly of a localized nature, that plays the major role in determining whether clinical fungous disease, such as acute attacks of fungous infection, occurs. The fact that fungi are readily, and probably continually, shed from the feet with clinical or subclinical infection [4] means that most individuals living in surroundings where dermatophytosis is prevalent are likely to have repeated exposure to pathogenic fungi. This explains why subclinical infection, often not discoverable even in repeated mycologic investigations, is so common. For how would one otherwise explain the recovery of one species of fungus from the feet of some of our volunteers when they had been exposed by us to another species and the finding of fungi in the foot-bath water of 12.5% of subjects clinically free from dermatophytosis.[4]

The common dermatophytes are "facultative pathogens" or "opportunists" that may be present on clinically healthy skin for a period of time. Only when conditions

for growth become favorable (i. e., lowered resistance of the host) may clinical disease result. A "fresh" exposure to fungi appears to be entirely unnecessary for the occurrence of clinical disease. The conclusion from these studies must be that individual hygiene, especially the use of methods designed to maintain and increase the resistance of the skin of the feet, is of the greatest importance for the prevention of fungous disease of the feet. On the other hand it may well be said that many of the accepted public health measures and procedures suggested by physicians to prevent epidemics of dermatophytosis are in all probability useless.

TABLE 3.—*Results of Mycologic Examinations of Twenty Subjects with Fungous Infection of Feet Exposed to Foot-Bath Water Contaminated with Fungi of Different Species Than That Causing the Natural Infection*

Volunteer No.	Natural Infection Due to	Exposed to	No. of Viable Fragments of Dermatophytes in Foot Bath * (200 Ml.)	Foot Examined	No. of Weeks After Attempt at Superinfection											
					1		2		3		4		5		6	
					KOH †	C.‡	KOH	C.	KOH	C.	KOH	C.	KOH	C.	KOH	C.
9	T. r.§	T. m.‖¶	.....	Exposed	+	T. r.	+	T. r.	+	T. r.	—	—	Not done		—	T. r.
				Control	+	—	—	T. r.	—	—	—	—			—	—
11	T. r.	T. m.	24,800	Exposed	—	—	—	—	+	—	—	T. r.	+	—	—	T. m.
				Control	—	—	+	—	—	—	+	—	+	—	+	T. r.
12	T. r.	T. m.¶	.....	Exposed	+	—	Not done		Not done		+	—	+	T. r.	—	T. r.
				Control	—	—					+	T. r.	—	—	—	—
14	T. r.	T. m.¶	.....	Exposed	+	—	+	—	—	—	+	—	+	—	+	—
				Control	—	—	+	—	—	—	—	—	—	—	—	—
19	T. r.	T. m.¶	.....	Exposed	—	—	—	—	—	—	+	—	+	—	+	—
				Control	+	—	—	—	+	—	+	—	+	—	+	—
25	T. r.	T. m.	34,600	Exposed	—	—	—	—	+	—	—	—	—	—	+	—
				Control	—	—	+	—	+	—	+	—	—	—	—	—
30	T. m.	T. r.	80	Exposed	+	T. m.	+	T. r.-T. m.	+	T. r.	+	T. m.	+	T. r.-T. m.	+	T. m.
				Control	—	—	+	—	+	—	+	—	+	—	—	—
31	T. m.	T. r.	670	Exposed	+	—	—	T. m.	—	T. m.	—	T. m.	—	T. m.	—	T. m.
				Control	—	—	—	T. m.	—	T. m.	—	T. m.	—	T. m.	—	T. m.
35	E. f.⁂	T. m.	6,800	Exposed	+	E. f.	+	E. f.	+	E. f.	+	E. f.	+	E. f.	—	E. f.
				Control	+	E. f.	+	E. f.	+	E. f.	+	—	—	E. f.	+	—
38	T. m.	T. r.	164	Exposed	—	T. m.	—	T. m.	—	—	—	—	—	T. m.	—	T. m.
				Control	+	—	+	—	+	T. m.	+	T. m.	—	T. m.	—	T. m
40	T. r.	T. m.	6,300	Exposed	+	—	+	—	+	—	—	—	—	T. r.	—	T. r.
				Control	+	—	+	—	+	T. r.	—	T. r.	—	T. r.	—	T. r.
48	T. r.	T. m.	37,400	Exposed	—	—	+	—	—	—	—	—	—	—	—	—
				Control	—	—	+	—	+	—	—	—	—	—	—	—
58	T. r.	T. m.	21,200	Exposed	—	—	+	T. r.	+	—	+	T. r.	—	T. r.	—	—
				Control	+	T. r.	—	—	—	—	—	—	—	—	—	—
65	T. m.	T. r.	428	Exposed	+	—	—	—	+	T. r.	+	T. r.	+	T. r.	+	T. r.
				Control	+	—	—	T. r.	+	—	+	T. r.	—	T. r.	—	T. r.
67	T. m.	T. r.	8,800	Exposed	+	—	—	—	+	T. m.	—	T. m.	+	T. m.	+	—
				Control	—	—	—	—	—	—	—	—	—	—	—	—
74	T. r.	T. m.	40,000	Exposed	+	—	—	—	—	T. r.	—	—	—	T. r.	—	T. r.
				Control	—	—	—	T. r.	—	T. r.	—	—	—	—	—	T. r.
79	T. m.	T. r.	64,200	Exposed	—	T. m.	+	T. m.	+	—	—	—	—	—	—	—
				Control	—	—	—	—	—	—	—	—	—	—	—	—
85	T. m.	T. r.	8,460	Exposed	—	T. m.	+	T. m.	+	T. m.	—	T. m.	+	T. m.	+	T. m.
				Control	—	T. m.	+	T. m.	+	T. m.	+	T. m.	+	T. m.	+	T. m.
103	T. r.	T. m.	28,000	Exposed	+	—	+	—	+	—	+	—	+	T. r.	+	—
				Control	+	—	+	—	+	—	+	—	+	—	—	—
106	T. m.	T. r.	530	Exposed	—	—	+	—	+	T. m.	—	—	+	—	—	—
				Control	—	—	—	—	+	T. r.	+	T. r.	—	—	—	—

* Calculated from plate counts of stirred suspensions.
† Potassium hydroxide mount.
‡ Culture.
§ Trichophyton rubrum.
‖ T. mentagrophytes.
¶ Exposed to foot-bath water contaminated by a person with active dermatophytosis.
⁂ Epidermophyton floccosum.

EXPERIMENTAL SUPERINFECTION WITH DERMATOPHYTE

Further experiments were conducted to answer a second question: Can the feet of subjects with a primary fungous infection due to one species of dermatophyte be deliberately superinfected with another species of dermatophyte?

Technique.—Twenty subjects from whose feet cultures of a dermatophyte had been isolated after at least one of two preliminary scrapings were exposed to foot-bath water contaminated with a species of fungus other than that causing the primary infections. The technique of exposure and of examination during the subsequent six weeks was the same as described above. Four subjects were exposed to the foot-bath water of persons with proved fungous disease of the feet, while 16 others were exposed to foot baths containing suspensions of dermatophyte cultures. The number of viable fungus particles added to each basin varied between 80 and 64,200, with an average of about 17,600.

Results.—The results obtained in 20 subjects are presented in table 3. In 12 subjects only the organism causing their primary, previously existing "natural" infection was isolated. From four subjects no cultures were isolated subsequent to exposure. Four subjects (no. 11, 30, 65, 106) are of particular interest because superinfection was apparently achieved. Subject no. 11 had a natural T. rubrum infection, but, following exposure to T. mentagrophytes, the latter fungus was isolated from

the exposed foot. Subject no. 30 had a "natural" T. mentagrophytes infection, but, following exposure to T. rubrum, both T. mentagrophytes and T. rubrum were isolated from the exposed foot. Subject no. 65 had a "natural" infection caused by T. mentagrophytes, but, after exposure to T. rubrum, this organism was isolated from both the exposed and the unexposed foot. Subject no. 106 had a "natural" infection caused by T. mentagrophytes, but, after exposure to T. rubrum, this organism was isolated from the unexposed foot.

Comment.—We succeeded in at least 4 of 20 attempts in producing a fungous superinfection in subjects with culturally proved fungous infection of the feet. The possibility exists that superinfection may have taken place in some of the remaining 16 subjects, but positive evidence is missing in the form of isolation in culture of the species of fungus used in the deliberate exposures. These findings are of importance because they show that, upon adequate exposure, superinfection can be deliberately induced in some subjects. This is in agreement with the many clinical reports of fungous infections with more than one species of dermatophyte. It should be noted, however, that neither these four nor any of the other volunteers in this experiment showed any clinically detectable change in the character of their infection. Moreover, our findings bring evidence, in addition to that presented in the previous experiment, that our methods of exposure were adequate to bring about at least temporary establishment of these facultative pathogens on the feet but that this did not produce any clinical disease.

The observation that more than one species of fungus was found on the feet of 4 of our 20 subjects raises the question of whether many more persons with dermatophytosis than has hitherto been thought harbor more than one species of dermatophyte on their feet. It appears possible that, if scrapings of the feet were taken repeatedly in many subjects, a much higher incidence of mixed infections might be found to exist.

In only one instance in 68 attempts (1.5%) were we able to produce a culturally proved infection in a person apparently free from dermatophytosis by deliberate exposure to fungus-contaminated foot baths as compared with 4 of 20 (20%) successful attempts at deliberate "superinfection." Although the series is small, these data could perhaps be interpreted to mean that the feet of persons with clinical fungous disease are inherently more susceptible than those free from clinical fungous disease to the at least temporary establishment of another species of dermatophyte.

SUMMARY AND CONCLUSIONS

Attempts were made to cause fungous disease in human volunteers apparently free from fungous infection by immersing their feet for 30 minutes in foot-bath water heavily contaminated with dermatophytes. Not a single instance of clinical fungous disease was produced among 68 human volunteers exposed under such conditions, despite the fact that fungous mycelia were found on one or both feet of 37 (54%) during the six weeks after fungous exposure (in 19 on the exposed foot, in 5 on the control foot, and in 13 on both feet). Attempts were made to produce superinfection in human volunteers with fungous infections by immersing their feet for 30 minutes in foot-bath water heavily contaminated with fungi of a different species. In at least 4 of the 20 fungus-infected subjects this led to superinfection.

It appears that it would be desirable in the future to differentiate sharply between "asymptomatic fungous infection" and "fungous disease" of the feet (dermatophytosis), since the common dermatophytes are "facultative pathogens" or "opportunists" that are often and perhaps usually present on clinically healthy skin and in such places as the nails and callouses of the feet. The role of these fungi in causing disease only when favorable local conditions prevail ("lowered resistance") may be likened to that played by Mycobacterium tuberculosis or Micrococcus pyogenes. Most individuals living in surroundings where fungous infection of the feet is prevalent may well have daily exposures to these facultatively pathogenic fungi. Under prevailing conditions exogenous exposure seems to be practically unpreventable. It plays at most a minor role in the causation of active attacks of fungous disease of the feet. It would appear that the public health and individual measures for prevention of active attacks of fungous disease of the feet must for the present be based on the maintenance and increase of local resistance to infection of the feet rather than on largely useless measures designed to prevent infection.

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Genetically Determined Disorders of the Renal Tubules.—In recent years a number of genetically determined disorders have been found to involve changes in renal tubule function. They include conditions as widely different clinically and biochemically . . . as cystinuria, vitamin-D resistant rickets, galactosaemia, Wilson's disease, and the Fanconi syndrome. . . . Active reabsorption by the renal tubule cells of a large number of different metabolites from the glomerular filtrate is known to occur. There appears to be a complex of different processes each handling one substance or a group of related substances, but no doubt integrated together at various levels. Abnormal genes are known which lead to a disturbance of this complicated transport system at different points so that the reabsorptive capacity of the tubules for particular metabolites or groups of metabolites is diminished. In some of these disorders the disturbance in renal tubular function is highly specific for a small group of metabolites or even a single metabolite, while the reabsorption of other substances goes on perfectly normally. For example in cystinuria there is a specific abnormality in the reabsorption of four amino acids; cystine, lysine, arginine and ornithine (Stein, 1951; Dent, Senior and Walshe, 1954). All the many other amino acids present in the glomerular filtrate are reabsorbed normally as are other substances. Similarly in renal glycosuria the defect is in most cases confined to glucose reabsorption (Govaerts, 1952) and in one type of vitamin-D resistant rickets to phosphate reabsorption (Dent, 1952). On the other hand in some conditions a more generalized disturbance of tubular function is encountered. In the Fanconi syndrome (Dent, 1952) a disturbance in tubular reabsorption occurs which involves many amino acids, glucose, phosphate, water and perhaps bicarbonate. In Wilson's disease the reabsorption of a large number of amino acids (Stein, Bearn and Moore, 1954), often glucose (Bearn and Kunkel, 1954), and occasionally perhaps uric acid (Bishop, Zimdahl and Talbott, 1954), may be affected. Thus it is apparent that abnormal genes may lead to dysfunction of the renal tubule transport system at many different levels. Now each of these conditions appears to be determined by an autosomal gene, though of course it is a different one in each case.—Prof. Clifford Wilson, D.M., F.R.C.P., Section of Experimental Medicine and Therapeutics, Discussion on the Renal Tubules, *Proceedings of the Royal Society of Medicine*, October, 1955.

THE BIOPHYSICAL BASIS OF PHYSICAL MEDICINE

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• ***Adequate heating of the deeper tissues without excessive heating of the superficial layers is one of the important problems in physical medicine. In their effects, ultrasonic vibration and microwave diathermy are closely related, although the former consists of longitudinal mechanical vibrations while the latter consists of transverse electromagnetic waves. Ultrasound provides highly effective depth of penetration in deep tissues having a high water content; microwaves are preferable in the case of bone structures.***

Dosage cannot be read simply from meters, because tissues vary in their absorption coefficients and reflection occurs at interfaces. In the case of ultrasound the dosage must be closely watched because the margin between effective and injurious doses is narrow. The transducers available at present for ultrasound give a small radiation field that limits its usefulness to very local application.

We may define physical medicine by its use of physical forms of energy for therapeutic and diagnostic purposes in medicine. The various forms of diathermy in use today have established an item of major importance in physical medicine. This paper attempts to evaluate present-day knowledge of diathermy, in order to establish the fundamentals characteristic of its various forms. The term "diathermy" is used throughout this paper to describe the clinical techniques employed to achieve "deep heating," i. e., heat development in the tissue beneath the skin and subcutaneous fatty layers by means of conversion of various forms of physical energy into heat. Sufficient deep heating will cause in the exposed part of the body temperature rise, consequent vasodilatation, and increase in cellular permeability and metabolic rate.[1]

Diathermy is indicated in cases where local increases in blood circulation and metabolic rate are considered beneficial. Ideal deep heating cannot be achieved effectively by "surface heating" as performed by application of local heat with warm water, heating pads, or infrared rays. The reason is that thermal flow from the heated body surface often has to overcome a more or less pronounced subcutaneous fatty layer, which possesses a comparatively poor heat conductivity and necessitates, therefore, substantial and often intolerable temperature rise in the surface of the skin in order to achieve sufficient heat transfer into the interior. Therefore, ideal deep heating must rely on its ability to transform certain forms of physical energy, which in themselves are not dangerous to the body tissues, into heat beneath the subcutaneous fatty material, with only minor heat loss in skin and fatty matter.

It is characteristic of the various forms of diathermy presently available that each of them, shortly after their acceptance by the medical profession, was overestimated in its performance. This happened with so-called ultrashort-wave diathermy, which is essentially the application of ultra-high-frequency currents for heating purposes. It happened to some extent with so-called microwave therapy, which is the application of electromagnetic radiation for heating purposes. Also, it occurs now with "ultrasonic therapy," i. e., the application of high frequency mechanical vibrations.

Overenthusiastic evaluation of any form of therapy must necessarily be followed by criticism. If this criticism becomes too great, it may blind our view to the real value of the therapy under consideration. I disagree with those authors who feel that ultrasonic therapy can do just about everything, only do it much better than can be done with all other forms of physical therapy. I prefer a position that emphasizes that each of the various forms of therapy available has its virtues and that we should strive for a clear recognition of the various indications for application of each form of diathermy. This opinion is based on an evaluation of purely biophysical considerations. I will attempt to summarize these arguments in the hope that they may stimulate corresponding work on the clinical level.

MODES OF ACTION OF SONIC AND ELECTRIC DIATHERMY

Important contributions have been made in pointing out the fact that the effects of various forms of physical energy utilized in diathermy are thermal ones and of a reversible nature, if we exclude destructive effects of high intensities. This has been discussed especially for the sonic case by Lehmann,[2] and the electrical case is summarized by Krusen.[3] It is justified, therefore, to restrict the total discussion, at least at present, to the thermal aspects of various forms of diathermy.

In the category of thermal effects, we differentiate between "selective," "structural," and "volume" heating.[4] I have shown that it is impossible to heat selectively volume fractions smaller than about 1 cu. mm.[4a] Therefore, here we can exclude definitely the possibility of selective

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1. Herrick, J. F., and Krusen, F. H.: Certain Physiologic and Pathologic Effects of Microwaves, Electrical Engin. **72**: 239, 1953. Richardson, A. W.; Imig, C. J.; Feucht, B. L., and Hines, H. M.: Relationship Between Deep Tissue Temperature and Blood Flow During Electromagnetic Irradiation, Arch. Phys. Med. **31**: 19, 1950.

2. Lehmann, J. F.: Biophysical Basis of Biologic Ultrasonic Reactions with Special Reference to Ultrasonic Therapy, Arch. Phys. Med. **34**: 139, 1953.

3. Krusen, F. H.: Physical Medicine: Employment of Physical Agents for Diagnosis and Therapy, Philadelphia, W. B. Saunders Company, 1941.

4. (*a*) Schwan, H. P., and Piersol, G. M.: Absorption of Electromagnetic Energy in Body Tissues: Review and Critical Analysis, Am. J. Phys. Med. **33**: 371, 1954. (*b*) Schwan, H. P., and Carstensen, E. L.: Advantages and Limitations of Ultrasonics in Medicine, J. A. M. A. **149**: 121 (May 10) 1952.

heating of bacteria and like objects. Structural heating, taking place at the interface of mediums with different indexes of refraction, occurs only in the case of sonic radiation. It is due to the transformation of part of the sonic energy into transverse waves, which are rapidly absorbed near the interface, and simulates truly selective heating of the interface per se. It partially explains temperature rise reported in bone structures.[5] The temperature build up in bone is obviously due in part to the fact that the interface between bone structure and surrounding muscular tissue, with vastly different acoustic impedance, heats up and creates a temperature barrier around the bone, whose existence in itself must yield temperature elevation in bone. In addition to this, it has been found by Hueter[6] that bone is a good sound absorber. This means that the fraction of sonic energy that penetrates into bone structures is effectively absorbed and transformed into heat.

A related phenomenon must be considered that may manifest itself in the sonic case as structural heating. When any type of wave, either sonic or electromagnetic, penetrates through a layer of material, this material may affect the wave propagation only when its thickness is comparable to or greater than the wave length of the radiation. At present, the wave length of clinically applied sound is near 1 mm. in tissue. This means that not only bone structure but also relatively thin pieces of connective tissue may influence the sound propagation. On the other hand, electromagnetic waves employed clinically operate with a wave length of about 12 cm. in air, i. e., a wave length of about 2 cm. in tissue. The propagation of such waves is less likely to be affected by inhomogeneous structure of tissue complexes. Thus, we recognize one of the important differences between sonic and electromagnetic radiation. Ultrasound causes strong structural heating, while microwave causes purely volume heating.

This basic difference between sonic and electromagnetic radiation can be extended from the macroscopic to the microscopic level. Electric energy now employed in medicine is of such high frequency that it floats unhindered through cell membranes and establishes a uniform heating rate of the intercellular and extracellular fluids.[4a] It has been shown, on the other hand, that a strong absorption of sound takes place in or around protein molecules, while the fluids inside and outside biological cells and surrounding the protein molecules themselves are poor sonic absorbers.[7] In addition, cell nuclei as a whole and cellular structure may contribute somewhat to the conversion of sonic energy into heat. In summary, sonic energy is transformed into heat through the solid components of the biological material and electric energy through the fluid components. Since the latter establish the bulk of the volume of the material, electric energy acts also on a microscopic level much less specifically than sonic energy.

5. Bender, L. F.; Herrick, J. F., and Krusen, F. H.: Temperatures Produced in Bone by Various Methods Used in Ultrasonic Therapy: Experimental Study, Arch. Phys. Med. **34**: 424, 1953.

6. Hueter, T. F., in Ballantine, H. T., and Bolt, R. H.: Quarterly Progress Report, Acoustics Laboratory, Boston, Massachusetts Institute of Technology, 1951, p. 38.

7. Carstensen, E. L., Li, K., and Schwan, H. P.: Determination of the Acoustic Properties of Blood and Its Components, J. Acoust. Soc. **25**: 286, 1953.

Even more important than this fundamental difference between sonic and electrical forms of diathermy is the discussion of the different acoustic and electric properties of various types of tissue and their effect on the performance of various forms of diathermy. This is obvious when we realize the following sequence of events: First comes the mechanism of absorption of the applied physical energy, i. e., its transfer into heat. This mechanism is defined completely by the material constants and the relative arrangement of the various biological mediums treated. It is expressed in physical symbols and, therefore, treated in the language of physics. Its investigation is a primary objective of biophysical research. Second comes the effect of the generated heat on physiological functions. Dilatation of blood vessels, change in metabolic rate, and change in excitability can be expected. Their recognition and understanding require physiological studies. Finally comes the clinical application of such physiological effects as may be produced by heat. This in its planning stage may be a matter of consultation between the practically interested physician and the physiologist. The ultimate success must be based on a great number of experiences, evaluated by a statistically trained physician. My primary objective here is to contribute to the first part of this program, i. e., to clarify the biophysical principles upon which performance of various forms of diathermy rests.

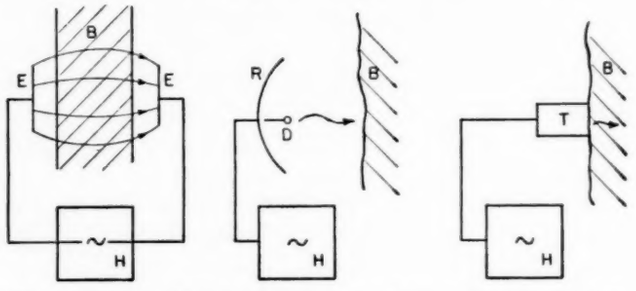

Fig. 1.—Characterization of presently available techniques for deep heating. *Left*, ultra-short-wave diathermy. A high frequency current is conducted from the high frequency generator, *H*, to the electrode, *E*, and passed through the body, *B*. *Center*, microwave therapy. Microwaves are generated by a dipole, *D*, and beamed into the body, *B*, with the help of a reflector, *R*. The dipole is energized from a high frequency generator. Microwave therapy in its present form utilizes "air-borne" radiation, i. e., the space between radiator and body is filled by air and the distance between the two not critical. *Right*, ultrasonic therapy. High frequency currents are transformed by a transducer, *T*, into vibrations, and these sent into the body. The transducer has to establish firm contact with the body to exclude any air between the two.

So far, three different techniques exist to approach the ideal of true deep heating; namely, heating with high frequency alternating electrical currents, commonly called ultra-short-wave therapy; heating with electromagnetic waves, so-called microwave therapy; and heating with ultrasonic waves, i. e., ultrasonic therapy. Each of these various types of diathermy utilizes a completely different form of energy (fig. 1). Ultra-short-wave diathermy and microwave diathermy both utilize electric energy for the transfer into heat, but they are different insofar as the first one utilizes electric current flow and the second one waves. Sonic and microwave diathermy both are similar in utilizing the absorption of waves, but the character of the waves is mechanical in the first case and electrical in the second case.

Performance-wise, ultrasonic and microwave diathermy are much more closely related than the two elec-

tric therapies. The more established ultra-short-wave therapy has been reviewed by many authors.[8] It provides deep heating only to a moderate extent (fig. 2). Spread of current, as the high frequency current enters into the body, emphasizes excessive heat development in the subcutaneous fatty tissue. Strong efforts have been made to minimize these disadvantages, and recent advances in electrode design have helped to provide the optimal depth effect obtainable with this form of diathermy.[9]

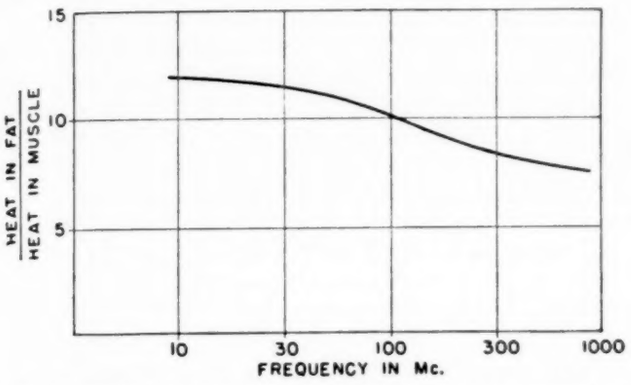

Fig. 2.—Specific heat development of subcutaneous fat as compared to that of muscular tissue beneath the subcutaneous layer by ultrashort waves. The curve shows the difficulties of achieving heating in the deep tissues with ultra-short-wave therapy. Mc. = megacycles.

Since we can assume that no significant improvement can be obtained with this form of diathermy, and, since the two more modern forms of diathermy (sonic and electromagnetic) can provide superior deep heating, (compare figure 2 with table 4), I shall restrict my discussion from here on to the two forms of radiation therapy with ultrasound and microwaves.

STANDARDS OF PERFORMANCE FOR ULTRASONIC AND ELECTROMAGNETIC RADIATION DIATHERMY

The performance of either type of radiation therapy is determined by three factors: 1. How far does the energy penetrate into the deep tissues? If the depth of penetration is too small, no deep effect can be achieved, and, if the depth of penetration is very large, the transfer from radiant into heat energy is insufficient to provide heat. Hence, depth of penetration values between about 1 to 3 in. seem most practical. 2. To what extent is the radiant energy capable of passing beyond the subcutaneous fat layer into the deep tissues without major energy loss? Interest in the heating of the subcutaneous fatty tissues with diathermy is small, since it can be achieved more easily by methods of surface heating and since its temperature rise is unimportant from a biological point of view. In the discussion of the influence of the subcutaneous fatty layer, we must consider: (*a*) how is the temperature increase in this tissue compared with the one achieved in the deep tissues and (*b*) what percentage of the total available energy is absorbed in the fatty and in the deep tissues? We are obviously interested in keeping the temperature rise and heat development in the subcutaneous fat low, in order to achieve truly deep heating. 3. How can we determine and reproduce the proper dosage that is biologically effective for the various forms of radiation diathermy and on what factors does it depend? The amount of energy produced by the energy source is determined easily by instruments provided with the generator. The energy that is biologically effective, i. e., that develops heat in the deep tissues beneath the subcutaneous fatty material, depends in a complicated manner on this equipment-registered energy. Part of the total energy is reflected back from the body surface and part is absorbed in the fatty material before it reaches the deep tissues of interest. The subjective feeling of the patient, relying on the response of the sensory elements in the skin, is an unreliable guide for the effectiveness of deep tissue heating, since the ratio of temperature rise in skin and deep tissue is a complicated function of type of radiant energy and such parameters as thickness of subcutaneous material between deep tissue and skin, effectiveness of surface cooling of skin, and frequency. It is, therefore, of importance to investigate the relationship between registered and biologically effective dosage before one can hope to obtain reproducible results with diathermy.

Knowledge of the coefficient of transmission, i. e., the energy that is not reflected from the body surface, and knowledge of the energy consumed in the subcutaneous tissue and depth of penetration in the deep tissues characterize the performance of any particular form of diathermy completely. These quantities are determined uniquely by the electrical and acoustic properties of various body tissues, and the electrical and acoustic properties of such tissues are summarized, therefore, briefly in the following section.

Electrical and Acoustic Properties of Body Tissues.—Measurements of the electrical properties of body tissues have been performed over the total frequency spectrum of interest. Their properties reflect the existence of two distinctly different types of tissue: tissues with high water content, such as muscle and all body organs, and tissues with low water content, such as fatty tissue, bone, and bone marrow. The electrical properties of tissues with high water content are reproducible within a few per cent and can be explained easily on the basis of their combined water and protein content.[4a]

TABLE 1.—*Electrical Properties of Muscular and Fatty Tissue for Various Frequencies of Microwave Therapy* *

	Megacycles			
	100	300	1,000	3,000
Dielectric Constant				
Muscle	130	100	80	45
Fatty tissue	1,500-4,000	1,000-3,000	700-2,500	500-1,000
Specific Resistance, Ohm-Cm.				
Muscle	75	60	50	45
Fatty tissue	5-8	4.5-7	4-6	3.5-5

* The data for muscular tissue are representative for all tissues with high water content, those for fatty tissue for bone and bone marrow. See footnote 4*a*.

The dielectric data for tissues with low water content are quite different and fluctuate considerably from sample to sample. Table 1 summarizes such data for the electric frequency range from 100 to 3,000 megacycles. The acoustic properties of tissue are less well established than

8. Paetzold, J., in Vilbig, F., and Zenneck, Z.: Advancements in High Frequency Techniques, Leipzig, Germany, Akademische Verlagsges., 1943, vol. 2, p. 763. Footnote 3.

9. Kebbel, W., and Pätzold, J.: Die Wärmeverteilung in Fett-Muskel-Schichten bei verschiedenen Spulenanordnungen, zugleich ein Beitrag zur Problematik der Mikrowellentherapie, Strahlentherapie **95**: 107, 1954.

the electrical ones; yet, enough is known from measurements of various types of tissue with high water content [10] and measurements of fatty material [11] to state a similar basic difference between the acoustic properties of tissues with high water content and fatty material. Table 2 summarizes such data. Bone, on the other hand, has an

TABLE 2.—*Absorption Coefficient in Muscle, Fat, and Bone*

	Absorption Coefficient, Megacycles		
	1	2	4
Muscle *	0.3	0.5	1
Fatty tissue	0.07	0.2	0.6
Bone	0.6-2	...	...

* Representative for other tissues with high water content.

unusual depth of penetration figure and does not, therefore, fit into the pattern suggested by the difference in water content.

Depth of Penetration.—Depth of penetration values have been calculated from known electric and acoustic data for various types of tissue.[12] Figure 3 shows depth of penetration of electromagnetic radiation as function of frequency for the two tissue classes of high and low water content. Figure 3 also gives the same quantities for the acoustic case. This figure demonstrates the similarity of electromagnetic and acoustic radiation. In both cases, the depth of penetration decreases with increasing frequency, and in both cases the depth of penetration in the fatty tissues with low water content is considerably greater than the depth of penetration in the deep body

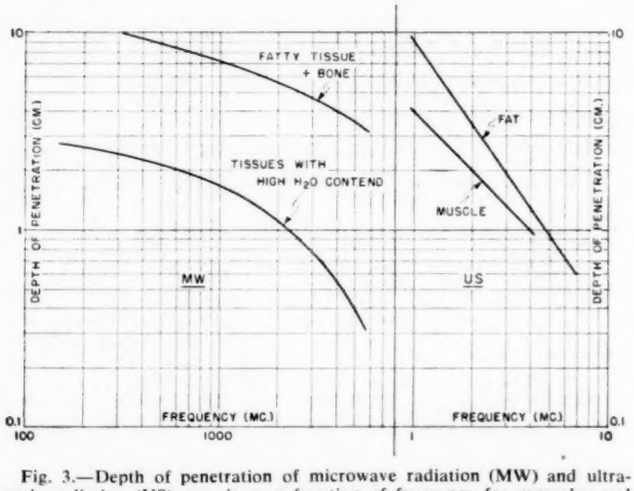

Fig. 3.—Depth of penetration of microwave radiation (MW) and ultrasonic radiation (US) are given as function of frequency for muscular and fatty tissue. The muscle data are characteristic for all tissues with high water content. Presently available ultrasonic equipment, operating near 1 megacycle (Mc.) has a greater depth effect than presently available microwave equipment, operating near 2,500 megacycles.

tissues with high water content. This indicates a preference of the radiation to heat the deep tissues of high water content if no energy is reflected backward from the interface of deep tissues and subcutaneous fatty matter.

10. Hüter, T.: Messung der Ultraschallabsorption in tierischen Geweben und ihre Abhängigkeit von der Frequenz, Naturwissenschaften **35**: 285, 1948. Pohlman, R.: The Absorption of Ultrasound in Human Tissue and Its Dependence on Frequency, Phys. Ztschr. **40**: 159, 1939.

11. Schwan, H. P.; Carstensen, E. L., and Li, K.: Heating of Fat and Muscle Layers by Electromagnetic and Ultrasonic Diathermy, Tr. Am. Inst. Electrical Engin., Communications and Electronics, **6**: 483, 1953.

12. Schwan, H. P.; Carstensen, E. L., and Li, K.: Comparative Evaluation of Electromagnetic and Ultrasonic Diathermy, Arch. Phys. Med. **35**: 13, 1954. Footnote 11.

Presently used ultrasonic equipment, operating near 1 megacycle provides practical depth of penetration in the deep tissues. The 1 megacycle penetration value of about 2 in. is large enough to provide depth effect and yet is not so large that no energy transfer into heat occurs. However, presently used microwave equipment, operating at 2,500 megacycles, does not penetrate beneath 1 cm. If its frequency were lowered to provide good depth of penetration similar to ultrasonic equipment, its frequency of about 2,500 megacycles should be decreased below 300 megacycles.

Were it only depth of penetration in the deep tissues that characterizes the efficiency of diathermy with radiation, the conclusion would be that commercially available ultrasonic equipment operates with about the best possible frequency, while the frequency of presently available microwave equipment is poorly chosen. Completely different conclusions are indicated, however, when the deep tissues are not of high water content but involve bone structure predominantly, such as in joints. Here electromagnetic radiation penetrates effectively (about 5 cm.), while sound of 1 megacycle is nearly as rapidly absorbed as is 2,500 megacycles microwave radiation in

TABLE 3.—*Ratio of Maximum Specific Heat Development per Volume Unit of Subcutaneous Fat and Deep Tissue*

Thickness of Subcutaneous Fat, Cm.	Megacycles		
	300	1,000	3,000
Microwave Therapy			
1	0.15	0.3	0.8
2	0.3	0.7	0.8
3	0.4	0.9	0.8
Ultrasound Therapy	1	2	
1	0.3	0.5	
2	0.32	0.6	
3	0.4	0.8	

muscular tissues. In summary, we may conclude that, in all cases where the deep tissues have high water content, ultrasound provides high effective depth of penetration, while in the case of bone structures microwaves seem preferable.

Energy Distribution in Subcutaneous Fat and Deep Tissues.—Knowledge of the electrical and acoustic properties of all important tissues permits analytic deduction of the rate of heat developed in subcutaneous fatty tissue and deep tissues.[12] Table 3 gives the results of such calculations. It gives the ratio of highest possible heat development per volume unit fat to the highest heat development per volume unit deep tissue. The table assumes deep tissues with high water content, i. e., material such as bone is presently not considered. The greatest possible specific heat development occurs, of course, in the deep tissue near its interface with the subcutaneous fat layer and in the fat near the interface of this tissue and skin. Density and specific heat of various types of tissue are comparable; hence it is possible to identify the ratio of heat developments, given in table 3 with the ratio of optimal temperatures in subcutaneous fat and deep tissue. This statement is true as long as heat conduction does not affect temperature distribution too much, i. e., it holds especially in the beginning of the treatment, when the total heat developed is mainly used for elevating the temperature at the site where it is pro-

duced. Therefore, table 3 gives at the same time the ratio of the speeds with which subcutaneous fat and deep tissues heat up in the early phase of the treatment. It follows from the numerical values in the table that specific heat development in subcutaneous fat and consequent temperature rise compares with that in deep tissues for presently used 2,500 megacycle microwaves if the subcutaneous fat layer is thicker than 1 cm. and with presently employed 1 megacycle sonic radiation if the fat layer thickness exceeds 3 cm.

Even more important than specific heat development and speed of temperature rise is the efficiency of the radiation to penetrate through the subcutaneous tissue into the deep tissue and there transform the major part of its energy into heat. The efficiency to penetrate effectively through subcutaneous fat and into the deep tissues is best characterized by the ratio of the total amount of heat developed in the deep tissues and the total amount of heat available. This ratio is given for various frequencies and thickness values of the subcutaneous fat in table 4. Tables 3 and 4 characterize some important features common to both ultrasonic and electromagnetic microwave diathermy: 1. The amount of energy loss and consequent heating in the subcutaneous fat increases with its thickness. 2. The efficiency in reaching into the deep tissues with the major part of the available energy decreases with increase in frequency. In the case of presently used 1 megacycle frequency in ultrasonic therapy, the subcutaneous fatty layer must be thicker than 2 in. in order to absorb more than 30% of the total energy that penetrates into the body. On the other hand, already a layer of 0.5 in. subcutaneous fat absorbs 30% of the microwave energy produced by presently commercially available instrumentation operating at 2,450 megacycles. In order to give equally good depth effect as produced by the sonic equipment, microwaves of a frequency of 400 megacycles are indicated. This again illustrates two things: 1. While the frequency used for optimum performance has been chosen with good insight into the biophysical mechanisms that are involved in the sonic case, this cannot be stated in the microwave case. 2. On the other hand, any statement that sonic energy must in general be superior for depth effect is wrong. Appropriate change in the microwave frequency makes microwave therapy again competitive with sonic radiation. That is, good performance of presently accessible sonic equipment in comparison with microwave equipment is due to unfortunate frequency choice in presently available microwave equipment and not due in general to an inferiority.

The discussions concerning the efficiency to penetrate into the deep tissues have assumed so far the existence of deep tissues predominantly of high water content. Different conclusions are derived when the deep tissues are made up of predominantly bony structures. In this case electromagnetic radiation penetrates freely from the subcutaneous material into the deep tissue, and the total amount of energy delivered into the deep tissue structures will be for presently used 2,500 megacycles greater than that developed in the subcutaneous fat as long as the subcutaneous fat layer is thinner than about 1.5 in. Even better depth effect is achieved with lower frequencies. On the other hand, sound waves penetrate just as unhindered from subcutaneous material into bone as into muscular tissue. This means that the results presented in table 4 apply also when the deep tissues are predominantly made up of bone structures. In comparing the microwave and the sonic radiation therapy, we may state that presently used frequencies are equally efficient in reaching into deep tissues when the deep tissue structures are of low water content, i. e., predominantly bone.

The efficiency to penetrate beyond the subcutaneous fat is of even greater importance than the depth of penetration in the deep tissues discussed previously. This statement is based on the fact that the heat developed in the subcutaneous fatty tissue contributes in all likelihood only to a small extent to desirable circulatory effects. Subcutaneous fatty tissue is poorly supplied with vessels, and the beneficial effects of vasodilatation, demonstrated to occur under the influence of energy absorption in the deep tissues,[1] must be small. Furthermore, most of the heat develops in the fatty tissues predominantly near its interface with the skin and will be conducted through the skin to the outside and eliminated for purposes of deep heating by the usual mechanism of temperature regulation of the human body. On the other hand, heat developed beneath the subcutaneous fatty material must increase the temperature of the deep tissues. It is separated by the relatively poor heat conducting subcutaneous fat from the surface, and, therefore, but little heat loss to the outside is possible. The total energy absorbed in the deep tissues is, therefore, available for effectively raising the temperature up to a point where a balance between generated heat and heat carried away by heat conduction is achieved. This balance can be achieved with presently available energies at a temperature elevation in the deep tissues that is not dangerous and yet provides a significant increase in blood flow. The substantial increase in circulatory activity is one of the important contributions to the understanding of the physiological effects of diathermy and emphasizes the necessity of getting the energy into the deep tissues without appreciable loss in the subcutaneous fatty material.

TABLE 4.—*Percentage of Total Energy That Reaches Tissues Beneath Subcutaneous Fat Layer*

Thickness of Subcutaneous Fat, Cm.	Microwave Therapy, Megacycles			Ultrasonic Therapy, Megacycles	
	300	1,000	3,000	1	2
1	97	90	70	93	80
2	90	70	45	86	66
3	80	55	40	80	55

Dosage Determination.—The third point of importance concerns the problem of proper dosage determination. Modern ultrasonic and microwave radiation equipment is provided with instruments that measure the total amount of energy produced by the equipment and irradiated against the body. However, a substantial part of this energy may be reflected from the body surface and is, therefore, not available for heating purposes. The amount of energy, as registered by the instrument, must be multiplied with the coefficient of reflection of the body surface to provide the biologically effective dosage. This value once again must be corrected in accordance with the values of table 4 in order to obtain the dosage avail-

able in the deep tissues from the instrument reading. Thus, the equation is obtained

$$\text{Deep tissue dosage} = R \times A \times \text{Registered dosage} \quad (1)$$

where A is the coefficient tabulated in table 4 and R the coefficient that determines what percentage of the instrument-generated energy is absorbed by the body. This latter coefficient can be calculated for the case of microwave therapy from the electrical properties of various tissues summarized in table 1. It is given as function of depth of subcutaneous fatty tissue and frequency for the electromagnetic case (microwaves) in figure 4. Assumptions underlying the calculation are that the total beam of radiation hits the body surface perpendicular under right angle and that deep tissues are of high water

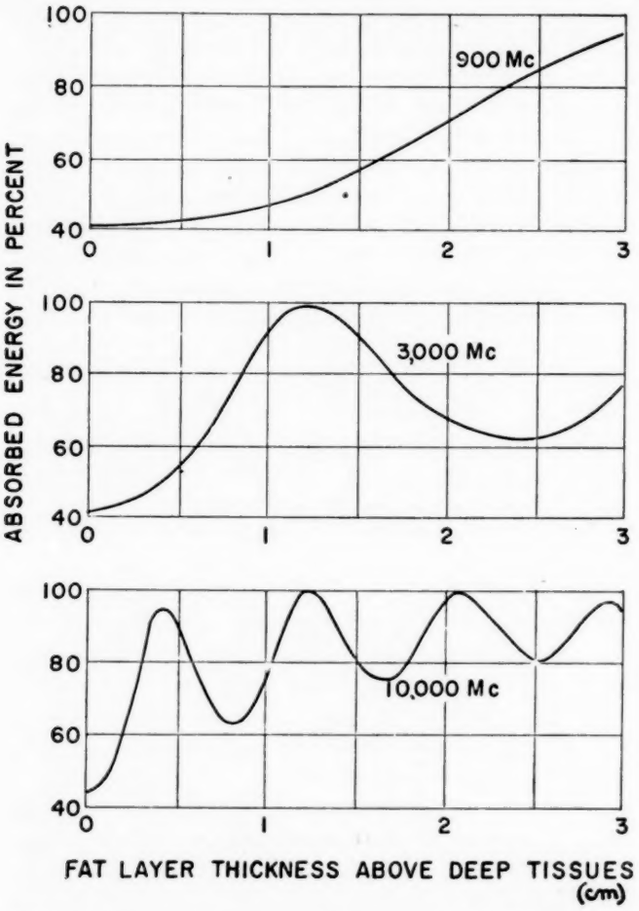

Fig. 4.—Percentage of air-borne microwave energy that is absorbed by the body plotted as function of thickness of subcutaneous layer (in centimeters) and frequency. Practical independence from the amount of subcutaneous tissues exists only for frequencies below 1,000 megacycles (Mc.).

content. It is seen that only at much lower frequencies than presently employed a predictable relationship independent from amount of subcutaneous fat exists. For this reason, frequencies not in excess of 900 megacycles are necessary to provide for realistic values of thickness of fat layer the possibility of prediction of deep tissue dosage from metered output. Under such circumstances the value A in table 4 becomes unity and the simple relationship

$$\text{Deep tissue dosage} = 0.4 \times \text{Registered dosage} \quad (2)$$

replaces the more complicated equation (1). In the case that the majority of the deep tissues are established by bone structures, a much simpler picture results. The amount of energy absorbed by the total body turns out to be independent of the thickness of the subcutaneous fat layer and is approximately independent of frequency. Its value is near that found above for low frequencies and can, therefore, again be characterized by the equation (2).

In the sonic case the transfer of energy depends solely on the effectiveness of the coupling of the sound transducer to the body. It is simply identical with 1, i. e., complete transfer of energy may be anticipated if close contact is provided between sound transducer and body, but only a tiny fraction of 1 if this intimate contact is not realized. This statement holds for any type of deep tissue. It is, however, one of the practical disadvantages of ultrasonic therapy that either constant attendance during the treatment is required to insure the necessary close coupling or a more elaborate underwater procedure is applied, where sound transducer and treated part of the body are immersed in water to provide a medium that transmits the sonic energy without loss into the body.

It is fortunate that the evaluation of the dosage problem leads to similar conclusions as derived before. Presently used sonic therapy, if properly applied, permits direct statement of the deep tissue dosage from the reading of the generator instrument. Commercially available microwave equipment does not permit this always, and a practically unpredictable and complicated relationship between measured and biologically effective dosage often exists that makes it difficult to establish dosage recommendations for clinical practice. However, this again is only due to poor frequency choice and is not related to any basic difference of sonic and microwave diathermy. Actually, if microwave equipment operating with frequencies below 1,000 megacycles were provided, deep dosage could be stated from instrument reading simply by multiplying with the factor 0.4. Close contact between the radiation source and the body surface would not be necessary, as it is unnecessary with present microwave equipment. That is, frequency alteration would provide physical medicine with equipment of similar performance to that provided by sound, however, without the disadvantage of the necessity of constant attendance.

Another disadvantage of sonic therapy is the limited size of the cross section of the radiation field, which rarely is larger than 10 or 20 sq. cm. This limitation is difficult to overcome since it is (*a*) difficult to provide transducers, i. e., soundheads in contact with the treated part of the body, with diameters much larger than 5 cm. and (*b*) almost impossible to establish the necessary close contact between body and transducer if the plane and rigid surface of the transducer is too large. The limited size of the cross section of the sonic field restricts its use to cases where very local application of heat is desired. However, such cases are rare, and sonic equipment necessitates, therefore, the application of a "massage" technique, where the soundhead is moved rhythmically over the total area of interest. This requires constant attention and makes it almost impossible to make any more than a qualitative statement concerning the biologically effective dosage for any part of the body, unless the movements of the soundhead are so well controlled that it is possible to state what percentage of the total time of treatment is spent by the soundhead over any part of the treated area.

I believe that the correct statement of dosage is in the sonic case of special importance in view of the small margin that is available between minimal dosage required for beneficial effect and maximal dosage, where damage occurs. The maximal dosage, where irreversible damage may occur, in all likelihood due to cavitation, has been reported at an output of 1 to 2 watts per square centimeter.[13] Minimal dosage needed for significant heating may be estimated to be at least 0.5 watts per square centimeter. Thus, the margin between necessary and dangerous dosage is in the ultrasonic case characterized by a factor of only 2 to 4. This is considerably less than available in the microwave case and is due to the fact that damage due to overheating occurs at a higher intensity level than damage due to cavitation, which can be induced only by sound.

Influence of Skin.—All of the above discussions have been based on an analysis of the influence of the subcutaneous fatty layer on the performance of sonic and microwave diathermy equipment. It has been assumed throughout that only the fatty layer separates the body surface from the deep tissues. I have assumed obviously that the skin that separates radiation source and body tissues is practically transparent for the radiation and does not affect its propagation. While no detailed measurements of the acoustic properties of skin have been performed so far, it can be stated from its composition that its acoustic properties must be quite similar to those of other deep tissues with high water content.

From this we may conclude safely that skin does not hinder the passage of sonic energy into the tissues beneath it and that it cannot affect seriously the amount of energy transformed into heat in subcutaneous fatty tissue and deep tissue. However, a small, well-defined amount of energy is transformed into heat in the skin, and the consequent temperature rise in skin may be noticeable. If this temperature rise and the associated excitation of the heat sensory organs in the skin are used to judge the applied dosage, serious misjudgment may occur concerning the available dosage in the deep tissues. Heat sensation serves, therefore, only as a poor substitute for dosage estimate with ultrasonic therapy. Since the amount of heat developed in the skin is small compared with the total amount of heat, all that has been stated about the dosage problem before would apply equally well if skin did not exist. Likewise, the statement concerning the depth of efficiency of sonic radiation is not affected by the presence of skin.

More complicated is the situation in the case of microwave radiation. Here the influence of skin can only be neglected if its thickness is very small compared with the electrical wave length in tissue.[14] This condition is fulfilled only when the frequency is below 1,000 megacycles. All statements above concerning depth efficiency and dosage apply for microwave radiation, therefore, only if lower frequencies than commercially available are utilized. However, it has been shown before that without skin the presence of the subcutaneous fat layer is sufficient to cause rather complicated dependence of depth efficiency and possibility of dosage determination on the thickness of the subcutaneous fat. The presence of skin appears complicating, therefore, only at such frequencies where already complex situations exist.

CONCLUSIONS

Both ultrasonic therapy and microwave therapy have greater depth effect than so-called ultra-short-wave diathermy. However, while the frequency for presently available ultrasonic equipment is well chosen, this cannot be stated for presently available microwave equipment. Depth of penetration in the deep tissues of the muscular type beneath subcutaneous fat, energy loss in the subcutaneous fat, and the possibility of administering with the so-called stationary treatment technique well-defined dosage favor the use of ultrasonic equipment. Presently available microwave equipment, on the other hand, is only capable of delivering heat into tissues with high water content beneath the subcutaneous fat layer when this layer is rather thin. Its depth of penetration in tissues of high water content is small, and the possibility of establishing from metered output the biologically effective depth dosage is limited seriously. However, if the presently used frequency of 2,500 megacycles is replaced by a frequency below 1,000 megacycles, microwave therapy becomes again competitive with sonic therapy.

On the other hand, microwave therapy has advantages. The upper energy level, where irreversible damage to tissues can occur, is higher than in the sonic case, and the margin between minimal effective dosage and maximal permissible dosage wider than in the sonic case. Its use is therefore recommended in the interest of the safety of the patient when relatively high dosage levels are indicated. The beam of radiation of microwave equipment is considerably broader than that available with ultrasonic equipment and permits the use of "stationary" techniques instead of the cumbersome massage technique now commonly employed with ultrasonic equipment. It furthermore provides adequate depth effect into tissues with low water content and is, therefore, indicated in the treatment of joints.

13. Lehmann, J. F., and Herrick, J. F.: Biologic Reactions to Cavitation, Consideration for Ultrasonic Therapy, Arch. Phys. Med. **34**: 86, 1953. Hug, O., and Pape, R.: Nachweis der Ultraschallkavitation im Gewebe, Strahlentherapie **94**: 79, 1954.

14. Foelsche, T.: Ueber die Energieverteilung im geschichteten Koerper bei Einstrahlung von dm- und cm-Wellen im Hinblick auf eine Waermetherapie, Ztschr. Naturforschung **9b**: 429, 1954.

Coronary Occlusion.—During the past thirty years the diagnosis of acute coronary occlusion has been greatly facilitated, and its treatment has been greatly improved. The diagnosis has been improved by the routine use of 12 electrocardiographic leads and by the recognition of atypical symptoms. Numerous mild cases have thereby been discovered, and a broader understanding of the disease has been reached. It should be emphasized that at the onset of the attack, possibly because the artery has not yet been completely occluded, the electrocardiogram may be normal or may show only slight changes. At this time RS-T depression may occur, as in coronary insufficiency, instead of the expected RS-T elevation. The RS-T elevation may not appear for hours and the Q waves only later, at the end of one to two days. The treatment of the disease has been improved by several major therapeutic advances. These include oxygen therapy, a low-calorie diet, the judicious use of digitalis and quinidine, the avoidance of such drugs as adrenalin, nitroglycerin, camphor, and strychnine, and the employment of anticoagulants. Recently Levine has advocated the chair treatment of coronary occlusion. In 1935 the mortality rate in our private patients during the first attack was 10 per cent. Today it is less than 5 per cent among such patients and is only 15 to 20 per cent during all attacks among ward patients.—Arthur M. Master, M.D., and Harry L. Jaffe, M.D., Treatment of Acute Coronary Occlusion, *New York State Journal of Medicine*, Nov. 15, 1955.

CLINICAL ASPECTS OF HYPERINSULINISM

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and
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• ***Hyperinsulinism in forms satisfying rigid diagnostic criteria was found in 91 cases. The attacks must be associated with exercise or fasting, the blood sugar level during an attack must be less than 50 mg. per 100 cc., and the attack must be relieved by the administration of sugar. Electroencephalograms do not help in the differential diagnosis. Fasting up to 72 hours is a valuable diagnostic test and has replaced the glucose tolerance test.***

Although hyperinsulinism is rare, it was found in all age groups from 9 to 72 years. A study of family histories indicated a positive relation to diabetes. The treatment is laparotomy and pancreatic exploration. In 76 of the 91 cases an actual tumor of the islet cells of the pancreas was found.

This paper reviews experience with patients who had hyperinsulinism seen at the Mayo Clinic during the years 1927 through 1953 and includes previously unreported long-term follow-up studies. Pathology,[1] diagnosis,[2] and differential diagnosis [3] of hyperinsulinism have been presented in previous reports and will not be dealt with in full here. Various reviews of this subject have appeared in recent years, the most complete being those of Howard, Moss, and Rhoads [4] and of Crain and Thorn.[5]

The term "hyperinsulinism" should be reserved for those patients in whom a hyperfunctioning tumor of the islets of Langerhans has been demonstrated or those who have received an injection of an excessive amount of insulin. This differentiates the condition from what we choose to call "functional" or "spontaneous hypoglycemia," discussed by Conn,[6] by Joslin and associates,[7] and by Lukens and associates.[8] Those cases due to overt or surreptitious injection of insulin [9] were excluded from this study. A total of 91 cases that fulfilled the rigid criteria of diagnosis as outlined by Wilder [2a] have been reviewed. Pathological criteria as outlined by Lopez-Kruger and Dockerty [1] are followed in the present report. These include (*a*) adenoma of the islets of Langerhans; (*b*) grade 1 adenocarcinoma of the islets of Langerhans; (*c*) obvious carcinoma of the islets with metastases; (*d*) no demonstrable lesion either at operation or at autopsy.

Hyperplasia of the islet cells, such as has been reported in the infants of diabetic mothers,[10] has been invoked by many authors as a cause of hyperinsulinism, but the pathological evidence for this condition is uncertain, and the condition is contrary to our experience. We agree with the statement by Warren and LeCompte [11]: "While it is generally assumed that diffuse hyperplasia of the islands may be a cause of hyperinsulinism, we are not aware of any case in which a completely convincing demonstration of this mechanism has been given. . . . Relief of symptoms in a patient following subtotal pancreatectomy is, of course, no reason for assuming the existence of hyperplasia." Nonfunctioning tumors of the islet cells may be found at operation or incidentally at autopsy. They may be benign or malignant, and they have been found in diabetic patients. The incidence of such tumors, benign or malignant, is one-half that of functioning tumors, according to the collected figures of Howard, Moss, and Rhoads,[4] but, with more careful routine postmortem study of the pancreas, they might be found more frequently than functioning tumors.

As will be seen later, all patients in this series given a diagnosis of "grade 1 adenocarcinoma" behaved, with one exception, as though they had benign adenomas. This man died 11 years after removal of his tumor in 1931, and his wife stated in a letter that a recurrence of his symptoms had developed one year prior to his death. No autopsy was performed. While there may have been recurrence of the original tumor, it is more probable that another tumor developed, as this occurred in two other cases in the series. Some patients with grade 1 adenocarcinoma survived and were well 14 years postoperatively. We have encountered seven cases of functioning metastasizing carcinoma of the islets, but have included no cases in which there was a nonfunctioning, metastasizing islet-cell carcinoma.

Fellow in Medicine, Mayo Foundation (Dr. Breidahl); from the Section of Surgery (Dr. Priestley) and the Section of Medicine (Dr. Rynearson), Mayo Clinic and Mayo Foundation.

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Dr. Breidahl was the Recipient of Flack Travelling Scholarship, from the Alfred Hospital, Melbourne, Australia.

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

The discussion of this paper was opened by Dr. Francis D. W. Lukens, Philadelphia.

1. Lopez-Kruger, R., and Dockerty, M. B.: Tumors of the Islets of Langerhans, Surg., Gynec. & Obst. **85**: 495-511 (Oct.) 1947.

2. (*a*) Wilder, R. M.: Clinical Diabetes Mellitus and Hyperinsulinism, Philadelphia, W. B. Saunders Company, 1940. (*b*) Gorsuch, M. T., and Rynearson, E. H.: Hyperinsulinism: The Use and Misuse of the Term, M. Clin. North America **28**: 985-990 (July) 1944.

3. Keating, F. R., Jr., and Wilder, R. M.: Spontaneous Hypoglycemia: Report of Cases, South. Med. & Surg. **103**: 125-131 (March) 1941. Skillern, P. G., and Rynearson, E. H.: Medical Aspects of Hypoglycemia, J. Clin. Endocrinol. **13**: 587-603 (May) 1953.

4. Howard, J. M.; Moss, N. H., and Rhoads, J. E.: Hyperinsulinism and Islet Cell Tumors of the Pancreas with 398 Recorded Tumors, abstracted, Surg., Gynec. & Obst. **90**: 417-455, 1950.

5. Crain, E. L., Jr., and Thorn, G. W.: Functioning Pancreatic Islet Cell Adenomas: A Review of the Literature and Presentation of 2 New Differential Tests, Medicine **28**: 427-447 (Dec.) 1949.

6. Conn, J. W.: The Diagnosis and Management of Spontaneous Hypoglycemia, J. A. M. A. **134**: 130-138 (May 10) 1947.

7. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 9, Philadelphia, Lea & Febiger, 1952.

8. Lukens, F. D. W.; Spoont, S., and Barol, S. R.: Hypoglycemia, J. Clin. Endocrinol. **14**: 248-254 (Feb.) 1954.

9. Rynearson, E. H.: Hyperinsulinism Among Malingerers, M. Clin. North America **31**: 477-480 (March) 1947.

10. Gordon, W. H.: Compensatory Hypertrophy and Hyperplasia of Islands of Langerhans in Utero: Congenital Hypoglycemia Due to Hyperinsulinism, Ohio M. J. **32**: 540-542 (June) 1936.

11. Warren, S., and LeCompte, P. M.: The Pathology of Diabetes Mellitus, ed. 3, Philadelphia, Lea & Febiger, 1952.

Multiple endocrine adenomas, previously reported by Underdahl and associates,[12] were discovered in eight patients with functioning islet-cell tumors, either prior to, at the time of, or subsequent to the removal of the latter. In the cases observed, adenomas of the thyroid, parathyroids, pituitary, and adrenals occurred singly or in combination.

TABLE 1.—*Pathological Findings and Sex Incidence in Hyperinsulinism*

Condition	Found at First Operation	Found at Biopsy from First Operation	Found at Second Operation	Found at Autopsy	Total	Sex	
						Male	Female
Adenoma.....	37	6	0	3	46	19	27
Grade 1 carcinoma.....	21	1	1	0	23	10	13
Metastasizing carcinoma.....	6	0	0	1	7	5	2
Normal pancreas	..	..	..	..	15	13	2

Hyperinsulinism has been encountered from childhood to late adult life. Age range of the patients in the present series was from 9 years to 72 years. The greatest incidence is in the fourth, fifth, and sixth decades of life.

At the suggestion of Dr. R. G. Sprague, a search was made to determine the incidence of a family history of diabetes in cases of hyperinsulinism. In 63 cases in which a definite statement was found, a positive family history for diabetes in a close blood relative was present in 15 cases and a negative one in 48. This is a percentage of positive cases of 24%, which is far higher than that of the general population. (Joslin and associates [7] quote the following figures: About 25% of diabetics have a positive family history for diabetes. About 3% to 6% of nondiabetics have a positive family history for diabetes.) It is of further interest that all patients with a positive family history had a proved islet-cell tumor. No patient was encountered in whom hyperinsulinism supervened after the development of diabetes, although such a sequence has been recorded (Bickel and associates [13]).

PATHOLOGY

The pathological findings in all 91 patients are listed in table 1. Thus, 76 patients had an insulin-producing tumor, while 15 patients had no demonstrable tumor

TABLE 2.—*Site of Origin in Pancreas of Islet-Cell Tumors*

Site of Origin	Adenoma	Grade 1 Carcinoma	Metastasizing Carcinoma	Total
Head.....	16	2	1	19
Body.....	12	9	1	22
Tail.....	17	9	2	28
Junction of body and tail...	0	2	2	4
Multiple.....	1	1	0	2
Not stated.....	0	0	1	1

at operation or at autopsy. We have no way of knowing how many of these 15 patients have tumors which were not found, but we must assume that tumors are present in many and they should be encouraged to undergo another operation. Table 1 also separates the patients by sex. There were 47 males and 44 females. Five males had metastasizing carcinoma, as compared to two females. Only 2 of 15 patients in whom a tumor was not found were females. We have no explanation for these differences.

The sites of origin of the tumors within the pancreas followed the distribution described by other authors (table 2). The ages of the patients at the time of their registration at the clinic are listed in table 3. Most of the tumors (57 of 76) and most of the "negative explorations" (12 of 15) involved patients between the ages of 30 and 59 years. The duration of symptoms prior to presenting for treatment (table 4) is longer on the average for those patients who had adenoma or grade 1 carcinoma than for those with metastasizing carcinoma. Even in the last group (metastasizing carcinoma) most patients experienced symptoms for more than one year before the diagnosis was established.

One patient on whom laparotomy was performed for hyperinsulinism in 1949 was found to have a "football-sized" tumor of the liver, considered at the time to be a spindle-cell sarcoma. There was no islet-cell tumor in the pancreas. In view of the recent report by Skillern and associates [14] the tissue was reviewed, and the revised diagnosis is islet-cell carcinoma with spindling of the cells. This case is therefore included as a metastasizing islet-cell carcinoma, since it had a typical clinical picture of hyperinsulinism.

TABLE 3.—*Age of Patients Having Islet-Cell Tumors*

Age, Yr.	Adenoma	Grade 1 Carcinoma	Metastasizing Carcinoma	Total Tumors	Normal Pancreas
Under 10.....	1	0	0	1	0
10-19.....	1	0	1	2	0
20-29.....	3	2	0	5	1
30-39.....	9	8	1	18	3
40-49.....	14	6	2	22	3
50-59.....	11	4	2	17	6
60-69.....	6	3	1	10	1
70 or over.....	1	0	0	1	1

CLINICAL SYMPTOMS

The symptoms of hyperinsulinism are those of hypoglycemia; these symptoms are widely known and recognized, and their mechanism of production has been investigated by many workers. The symptoms of an insulin reaction usually begin in a mild, sometimes hardly noticeable manner, with nervousness, apprehension, and hunger. If unrecognized and untreated the symptoms become more marked, and sweating, tremor, diplopia, and other symptoms of involvement of the nervous system develop; these may progress to manic behavior or to unconsciousness and convulsions. In hyperinsulinism it is the patient's story of the circumstances of the attacks that is important. The attacks occur after periods of fasting or vigorous physical exertion and thus are most frequently described as coming on late in the afternoon,

12. Underdahl, L. O.; Woolner, L. B., and Black, B. M.: Multiple Endocrine Adenomas: Report of 8 Cases in Which the Parathyroids, Pituitary and Pancreatic Islets Were Involved, J. Clin. Endocrinol. **13**: 20-47 (Jan.) 1953.

13. Bickel, G.; Mozer, J. J., and Junet, R.: Diabète avec dénutrition grave: Disparition de la glycosurie et atténuation progressive de l'hyperglycémie à la suite du développement d'un carcinome insulaire du pancréas avec métastases hépatiques massives, Bull. et. mém. Soc. méd. d. hôp. de Paris **51**: 12-21 (Jan.) 1935.

14. Skillern, P. G.; McCormack, L. J.; Hewlett, J. S., and Crile, George, Jr.: Hyperinsulinism Due to Islet-Cell Tumors Simulating Sarcoma: A Report of 2 Cases of Large Tumors Composed of Round and Spindle Cells Associated with Hypoglycemia, Diabetes **3**: 133-140 (March-April) 1954.

when a meal is missed, or on awakening in the morning. The early morning hours are the most usual for attacks of hypoglycemia in hyperinsulinism (table 5).

Spontaneous recovery from attacks of hypoglycemia in hyperinsulinism will occur, but usually the patient is given food or sugar. One patient was unconscious for about six to eight hours before recovering spontaneously.

TABLE 4.—*Duration of Symptoms of Islet-Cell Tumors*

Duration	Adenoma	Grade 1 Carcinoma	Metastasizing Carcinoma	Total Tumors	Normal Pancreas
Under 6 mo.	5	4	3	12	2
6-12 mo.	6	4	0	10	2
1- 2 yr.	10	5	4	19	5
3- 4 yr.	12	5	0	17	5
5- 6 yr.	7	3	0	10	0
7-10 yr.	5	2	0	7	0
10 yr. or more	1	0	0	1	1

The attacks are invariably relieved by the ingestion or injection of sugar in one form or another, and the speed of relief varies, naturally, with the severity of the attack, from a few minutes to half an hour or more. Many patients find, or are told, that they can prevent attacks by eating frequently and are thus on programs of three-hourly or four-hourly feedings, with occasional patients saying they must set an alarm clock for a 2 a.m. feeding if they wish to prevent prebreakfast attacks. With the frequent and large feedings, the patients are usually overweight when they present themselves for surgical treatment, but this is variable, and the condition produces such nervous stress in some individuals that they lose weight.

The symptoms may occur slowly or suddenly and may or may not be associated with loss of consciousness. The same pattern of symptomatology is usually constant for any one individual, although the severity may vary from attack to attack. It would appear as though some tumors secrete insulin constantly, as would be expected, and thus attacks occur at the same time every day. But other tumors appear to have intermittent secretion, paroxysmal attacks occurring at irregular and infrequent intervals.

Frequent, severe attacks with unconsciousness may be associated with temporary or permanent neurological symptoms, and a progressive mental deterioration may be seen in long-standing cases. Sweating attacks were the presenting complaint in 5 patients, 3 of whom had

TABLE 5.—*Occurrence of Early Morning Attacks of Hypoglycemia in Hyperinsulinism*

Early Morning Attacks	Tumor	No Tumor	Total
Positive	47	5	52
Negative	2	2	4
Not stated	27	8	35

tumors, but 11 patients (9 with tumors) had no sweating associated with their attacks. Coma occurred in 57 cases, was the presenting complaint in 27, and was associated with convulsions in 37. No correlation could be drawn between the type, frequency, or severity of symptoms and the subsequently found presence or absence of a tumor.

LABORATORY DATA

The figures for the highest fasting blood sugar value and the lowest blood sugar value obtained during an attack are given in tables 6 and 7. It is obvious that not all patients who have hyperinsulinism have a low fasting blood sugar value on random observation and that no correlation can be drawn between the level of blood sugar during an attack and the type of lesion present. In general, one expects a blood sugar value below 40 mg. per 100 cc. during an attack, but patients with tumors have had attacks with no blood sugar values below 40 mg. per 100 cc. On the other hand, an occasional patient may be alert and rational with blood sugar levels in the low thirties.

The glucose tolerance test has not proved of value in the diagnosis of hyperinsulinism. The results are too variable and difficult to interpret, and the fasting test has now replaced the glucose tolerance test. We do not believe that nervous patients with vague symptoms

TABLE 6.—*Highest Overnight Fasting Blood Sugar Level*

Concentration of Sugar, Mg./100 Cc. of Blood	Adenoma	Grade 1 Carcinoma	Metastasizing Carcinoma	Normal Pancreas
25 or less	0	0	0	0
26-35	1	2	0	0
36-45	10	5	2	1
46-55	13	2	2	2
56-65	9	6	1	6
More than 65	12	7	2	6
In normal range *	8	0	0	3
No record	1	1	0	0

* Included in class "more than 65."

TABLE 7.—*Lowest Blood Sugar Level During an Attack*

Concentration of Sugar, Mg./100 Cc. of Blood	Adenoma	Grade 1 Carcinoma	Metastasizing Carcinoma	Normal Pancreas
20 or less	0	0	0	0
21-25	7	5	0	1
26-30	9	7	5	2
31-35	13	8	2	3
36-40	11	2	0	7
41-45	5	1	0	1
More than 45	0	0	0	1
No record	1	0	0	0

should be diagnosed as having hyperinsulinism simply because varying degrees of hypoglycemia develop some hours after the ingestion of glucose. Likewise, the insulin tolerance test and the response to epinephrine have been found too variable to be of help in the diagnosis of hyperinsulinism.

DIAGNOSIS

The diagnosis of hyperinsulinism is often difficult, and the physician should remember its incidence when dealing with obscure cases of coma, confusion, or convulsions. Many of our patients received the correct diagnosis in the section of neurology and psychiatry, where they had been referred because of the history of convulsions and other neurological disturbances. The history of the attacks is the most important factor in making the diagnosis and needs to be gone into in great detail. The circumstances of the first attack; the circumstances of subsequent attacks; the relation, constant or incon-

stant, to fasting, exertion, and emotion; the presence or absence of early morning episodes, and the relief, and speed thereof, with food or sugar are essential features of the history.

The physical examination is noncontributory, except in so far as it may help to rule out evidence of other diseases that may cause hypoglycemia. The diagnosis is made on the fulfillment of the following criteria enunciated by Whipple [15]: (1) history of attacks associated with fasting or with exercise, or with both; (2) blood sugar value during an attack less than 50 mg. per 100 cc.; (3) attacks promptly relieved by the administration of glucose by mouth or dextrose by vein.

As has been seen, the values for fasting blood sugar levels may be in the normal range, and frequent determinations may be necessary. The intolerance for fasting forms the basis for the most satisfactory diagnostic procedure we possess, and it is the one on which we place most reliance. The patient is hospitalized and supervised during a period of deprivation of food for up to 72 hours. Water and tea or coffee without sugar or cream are allowed ad libitum. At the first sign of an attack, a blood sugar determination is made, and the patient is then under constant supervision until the physician decides to terminate the test. Frequently, multiple blood sugar determinations are made, and the finding of a value of less than 40 mg. per 100 cc. in the presence of hypoglycemic symptoms relieved by the intravenous injection of dextrose is diagnostic.

Occasional patients are encountered in whom a blood sugar value may be below 40 mg. per 100 cc. without symptoms. One such recent patient was a 32-year-old woman who had been known to have low blood sugar values at the time of "peculiar spells" for six months. While at the clinic she was fasted for 72 hours, and at the end of that time had a blood sugar value of 38 mg. per 100 cc. with no symptoms whatsoever. Her symptoms bore no relationship to the level of blood sugar and were not relieved by food or glucose. The diagnosis of hyperinsulinism was not sustained, and she is being observed on a medical program.

The results of the fasting test carried out at the clinic are given in table 8. We have records on the effect of fasting in 73 cases, and in 5 other cases it was observed that the attacks were occurring so frequently that it was unnecessary to fast the patient. Some interesting results, which cannot be clearly shown on the table, were obtained. One patient who had a carcinoma with hepatic metastases was at one stage able to go for 32 hours without food before symptoms developed and yet on a later occasion was having symptoms after 6 hours. Only one patient with a tumor was able to withstand a fast lasting more than 48 hours, and she went for 53 hours before symptoms of hypoglycemia developed. Three patients with islet-cell tumors were, on their original fasts, able to withstand food deprivation for 48 hours, but all subsequently developed symptoms within a shorter interval. One particularly puzzling patient was fasted to 48 hours on three occasions and yet had symptoms earlier than this on other occasions. She had a small grade 1 adenocarcinoma of the islet cells.

In general, there was no correlation between the type of lesion and the ability to withstand food deprivation. Patients with tumors may not develop symptoms during a 48-hour fast, and patients in whom no tumor can be demonstrated may develop symptoms and have a low blood sugar value within 12 hours. The longer the patient is able to go without food, the slower in onset and less definite in nature are the hypoglycemic symptoms. The fact that some patients with tumors can at times withstand prolonged fast tends to give credence to the hypothesis that some tumors may exhibit intermittent insulin secretion. Thus one or more negative 72-hour fasts are necessary to satisfactorily exclude the presence of hyperinsulinism, and the number of fasts necessary will be determined in each case by the patient's history.

DIFFERENTIAL DIAGNOSIS

A blood sugar value should be estimated in all cases presenting with convulsions or epilepsy, preferably during or just after an attack, and the history of the episodes should be scanned for features suggesting hyperinsulinism. Electroencephalography is of little diagnostic help, since abnormal tracings are obtained from patients who have had frequent hypoglycemic attacks as well as from those with lesions of the central nervous system of other origin.

TABLE 8.—*Fasting Test in Seventy-Three Cases* of Hyperinsulinism*

Condition	Duration of Fasting: 12 Hr. or Less	13-24 Hr.	25-36 Hr.	37-48 Hr.	More Than 48 Hr.	Negative	Too Many Attacks to Fast
Adenoma	15	18	3	4	1	0	1
Grade 1 carcinoma	7	6	3	2	0	0	1
Metastasizing carcinoma	2	0	0	0	0	0	3
Normal pancreas	4	3	4	0	0	1†	0
Total	28	27	10	6	1	1	5

* Not including last column of table.
† This patient was fasted and exercised for 24 hours and had a blood sugar value of 50 mg. per 100 cc. at the end.

The hypoglycemia of hepatic disease may closely resemble that of hyperinsulinism and therefore may obscure the diagnosis unless a history of liver disease is obtained. The clinical features are very similar, and there were some patients at the clinic who underwent laparotomy for suspected hyperinsulinism and who were found to have an otherwise asymptomatic hepatic cirrhosis. It is suggested that liver function tests be performed on those patients in whom the physician suspects that the hypoglycemia might be on the basis of hepatic disease. Fasting hypoglycemia, even with a fatal termination, is a well-recognized but infrequent accompaniment of conditions associated with hypofunction of the anterior pituitary or adrenals. There are usually other stigmas of these conditions, but the hypoglycemia may be the presenting or outstanding complaint. Hypothalamic lesions are rare causes of hypoglycemia.

It is often extremely difficult to differentiate hyperinsulinism from functional or nervous hypoglycemia. While the evidence for the existence of this condition is

15. Whipple, A. O.: Present-Day Surgery of the Pancreas, New England J. Med. **226**: 515-526 (March 26) 1942.

well substantiated, in our experience the condition is not common, and we have seen very few patients with a so-called "nervous hypoglycemia" in whom the blood sugar level drops much below 60 mg. per 100 cc. These patients usually give a history which is quite different from that of hyperinsulinism, in that it occurs in emotionally unstable individuals who tend to have weak or fainting spells with rapid, spontaneous recovery. They rarely have nocturnal symptoms, they do not have convulsive seizures, and the symptoms usually follow the taking of food, and not fasting. The symptoms are more referable to the sympathetic nervous system than to the blood sugar value.

Alimentary hypoglycemia, which is seen in patients who have undergone gastroenterostomy or gastric resection, is similar to the nervous type of functional hypoglycemia and needs to be distinguished from the dumping syndrome. This last presents symptoms resembling those of hypoglycemia but occurs within 15 to 30 minutes (sometimes reported as 1 to 2 hours) after the taking of food and is rarely associated with a very low blood sugar value.

TABLE 9.—*Diagnoses in Patients with Hyperinsulinism (Before the Correct Diagnosis Was Made)*

Diagnosis	Cases
Epilepsy	14
Tetany	2
Chronic nervous exhaustion	6
Cerebrovascular accident	4
Psychosis	6
Hysteria	4
Menopause	3
Brain tumor	2
Diabetes	2
Accused of being drunk	2
Heart attacks	1

In recent years McQuarrie and his associates [16] have described a condition which they term "spontaneously occurring hypoglycemia in infants." The symptoms are those of profound hypoglycemic shock, and the condition resembles hyperinsulinism to such an extent that pancreatic resection was undertaken in the earlier cases. Histological studies revealed an absence of the alpha cells of the pancreas, and recently it has been found that corticotropin (ACTH) is effective in controlling the condition.

Because of the vague and bizarre symptomatology of the hypoglycemic attacks of hyperinsulinism, early diagnosis is often difficult. Table 9 lists the diagnoses with which the patients with hyperinsulinism reported in this paper presented themselves at the clinic. It is only fair to state that two patients in the series had their initial attacks diagnosed as chronic nervous exhaustion at the clinic, but later the true nature of the illness was diagnosed and the hyperinsulinism was treated.

COMPLICATIONS

There may be no complications from the hypoglycemic attacks, or there may be permanent neurological or mental damage. Seven of these patients with hyperinsulinism experienced a distal progressive muscular atrophy secondary to a motor neuronitis. Removal of the pancreatic adenoma caused an arrest of the progression of the atrophy, although there was only minimal return of function. A report on these patients will be made at a later date by Dr. D. W. Mulder. Residual hemiparesis was noticed in 2 of the 91 cases and mental deterioration in 6. The illness may be fatal if left untreated, since death may occur due to hypoglycemia or due to an accident or fall when the patient is in hypoglycemic coma.

TREATMENT

The treatment of choice, once the diagnosis is firmly established, is laparotomy and pancreatic exploration. Some patients may refuse operation, and others, with mild symptoms, may elect to try a medical regimen before resorting to surgical treatment. The medical program consists of frequent feedings of a high-protein diet, with between-meal feedings if necessary. This program may be adequate to prevent attacks but results in a rapid gain of weight and is intolerable for long periods on this account. Use of corticotropin, as advised by McQuarrie for hypoglycemic infants, could be investigated. As soon as surgical treatment is decided on, the physician or the surgeon should have a long, frank talk with the patient and relatives to discuss the possible operative findings and to forewarn on the possibility of a partial pancreatectomy being performed. The patient is sent to the operating room with an intravenous solution of dextrose running or ready.

Surgical Procedures.—The present study incorporates a review of 91 patients who exhibited definite evidence of hyperinsulinism. As stated previously, patients in whom this diagnosis has been equivocal in any way have been excluded from consideration. Some of these patients had undergone operation on the pancreas prior to their first operation at the clinic, and a few had subsequent operations performed at the clinic and elsewhere. The first operation performed at the clinic was the one considered as the "first" operation in the present review.

Various operations were performed in the group of 91 patients, as follows: An islet-cell adenoma was excised in 48, partial pancreatectomy was performed in 26, total pancreatectomy was carried out in 3, and other procedures were performed in the remaining 14 patients. The latter group included six patients in whom only biopsy was accomplished for what proved to be an inoperable malignant lesion. In one case exploration was performed, but subsequently partial pancreatectomy with removal of the tumor was done. Biopsy of the pancreas was performed in four patients from areas suspected of showing tumor, but only normal pancreatic tissue was revealed in microscopic study of the resected tissue. Of the remaining three patients, all of whom underwent operation some years ago, ligation of the pancreas was performed in two and "decapsulation" in one. Neither of these procedures is recommended today.

A tumor of the islet cells was found at the first operation in 64 of these 91 patients (70%). In 48 patients (53% of 91) the tumor was removed by local excision, whereas in 10 patients partial pancreatectomy was required for satisfactory surgical extirpation of the lesion.

16. McQuarrie, Irvine: Idiopathic Spontaneously Occurring Hypoglycemia in Infants: Clinical Significance of Problem and Treatment, A. M. A. Am. J. Dis. Child. **87**: 399-428 (April) 1954.

Six of the 64 patients in whom an islet-cell tumor was found had a malignant type of lesion considered to be inoperable either because of local extension or the presence of metastases. In these six patients only a biopsy of the tumor was taken, and the lesion was not removed. More than one adenoma was found at the first operation in two patients. Two of the patients who had malignant lesions had multiple lesions in the pancreas.

In 27 of the 91 patients no tumor was seen or palpated at the time of the first surgical exploration. Pursuant to the plan of treatment outlined previously, partial pancreatectomy was performed in 17 of these 27 patients, and in 7 of these patients a tumor was discovered by the pathologist in the resected portion of the pancreas. Total pancreatectomy was performed in 3 of these 27 patients. Operation had been performed previously in two of these patients, at which time a portion of the pancreas had been resected. Symptoms had persisted which subsequently led to more radical surgical treatment.

Considering the findings in the entire group of 91 patients, it is noted that an actual tumor of the islet cells was present in 76 of the entire group. This tumor was found by the surgeon at the time of the first operation in 64 patients, by the pathologist in the resected pancreas or portion thereof but not by the surgeon at the time of operation in 7 patients, by the surgeon at a second operation in one patient, and by the pathologist at the time of autopsy in 4 patients. It is thus apparent that a small tumor of the islet cell may be difficult of identification by the surgeon, and its recognition actually may require extremely careful and even repeated examination on the part of the pathologist.

Of the 27 patients who had no tumor discovered at the time of the first surgical exploration, 12 had tumors subsequently discovered by the surgeon at a second operation or by the pathologist on examination of the resected tissue or at autopsy, and 15 had no tumors discovered at any time. This of course does not necessarily mean that actually no tumor was present in any of these patients, but at least none was demonstrable.

Postoperative hyperglycemia which persisted for more than 48 hours developed in 17 of the 48 patients in whom an islet-cell tumor was excised locally and in 15 of the 26 patients in whom partial pancreatectomy was performed. In 11 of these 15 patients the removed specimen of pancreas contained a tumor. The longest period that postoperative hyperglycemia persisted in any patient was two weeks, except of course in those patients in whom total pancreatectomy was performed. It is not surprising that hyperglycemia should develop and persist for a variable period after removal of a functioning islet-cell tumor, owing to temporary lack of function of the remaining islet-cell tissue. A comparable situation exists, for example, after removal of a functioning adenoma of the adrenal cortex in that temporary adrenal insufficiency ensues which necessitates appropriate treatment.

There were 7 postoperative deaths in the entire group of 91 patients. There were 4 postoperative deaths in the group of 48 patients in whom local excision of the tumor was performed. There was only one postoperative death in the group of 26 patients in whom partial pancreatectomy was carried out. One of the remaining two patients died after a total pancreatectomy; one died after biopsy study of a suspicious area of the head of the pancreas. Most of the postoperative deaths occurred some few years ago, and in fact there has been only one death in the 46 patients operated on since 1946. Pulmonary complications appeared to be the main contributory cause of death in four of the seven patients. Pancreatitis with or without fat necrosis and peritonitis was responsible for two deaths, and one patient who underwent total pancreatectomy in 1943 died on the operating table.

Late Results.—Results after operation for the entire group of 91 patients are indicated in table 10. It is to be hoped and expected that the mortality rate will be lower in the future than it has been in the past, which would make it appear likely that at least 70% or more of patients who undergo operation might expect cure after the first operation. It is also apparent that the incidence of recurrence after an apparent "cure" is quite low (3%). Further observations of late results may be considered in relation to the type of lesion that was present or the type of operation that was performed.

TABLE 10.—*Late Results in Relation to Type of Lesion in Ninety-One Patients*

Condition	Patients	Post-operative Death	Cure	"Cure" with Later Recurrence	Persistence
Adenoma	46	4	39	2	1
Grade 1 carcinoma	23	3	17	1	2
Metastasizing carcinoma	7	0	0	0	7
Normal pancreas	15	0	3	0	12
Total	91	7	59	3	22

If one considers the results after removal of an adenoma of the islet cells, it is seen that the prospects for cure are quite good (table 10). In two patients who had adenomas removed recurrence developed. One of these occurred one year later and the other seven years later. Both of these patients had a subsequent operation performed with removal of the recurrent adenoma and were cured after this second operation. It is interesting to note that the patient who developed recurring symptoms one year after operation subsequently underwent partial pancreatectomy. The pathologist diagnosed "adenomatosis" of the tail of the pancreas, the only such case in the series. At the present time this patient has remained cured for 11 years. One of the group experienced persistence of symptoms after removal of a single adenoma. Reoperation six months later failed to reveal an adenoma, and symptoms were still present when the patient was last heard from six years after the second operation.

The diagnosis of "grade 1 carcinoma" in an adenoma is perhaps an equivocal diagnosis even among pathologists. Twenty-three patients had lesions so diagnosed, however, and it is noted (table 10) that 17 of these patients remained cured. One patient was "cured" for a period of 10 years and then developed recurrence of symptoms and died one year later, without further operation. Two patients experienced persistence of symptoms

presumably because of an undetected lesion which was not removed. None of the seven patients who had metastasizing carcinoma of the islet cells was cured. All had persistence of symptoms and subsequently died.

The group of 15 patients who had no lesion of the islet cells discovered at the first operation, either by the surgeon or by the pathologist, is an interesting group. Three of these 15 patients were cured by partial pancreatectomy. Why this should be is not clear. The remaining 12 patients manifested persistence of symptoms. Four of these patients have had subsequent operations, one patient having had as many as four operations in all. In only one of these patients was a lesion subsequently found, removed, and the patient cured. The remaining three of these four have had persistence of symptoms despite removal of additional pancreatic tissue. One of these three patients died seven years after the last of four operations and was found to have an adenoma of the islet cells located in the remnant of the head of the pancreas. The surgeon always should be mindful of the possibility of ectopic pancreas when exploration of the pancreas reveals negative findings.

TABLE 11.—*Late Results in Relation to Type of Operation Performed in Ninety-One Patients*

Type of Operation	Patients	Postoperative Death	Cure	"Cure" with Later Recurrence	Persistence
Local excision	48	4	40	3	1
Partial pancreatectomy with removal of tumor	15	1	14	0	0
Partial pancreatectomy without removal of tumor	11	0	3	0	8
Total pancreatectomy	3	1	2	0	0
Other surgical procedures	14	1	0	0	13
Total	91	7	59	3	22

Late results also may be studied in relation to the type of operation that was performed (table 11). It is thus seen that local excision of an adenoma, if one can be found, is followed by results which are substantially as favorable as removal of such a lesion by partial pancreatectomy. In contrast, partial pancreatectomy, without simultaneous removal of an adenoma, does not give a good result except in a very limited number of patients. The two patients who survived total pancreatectomy are alive and well 10 and 12 years after operation. One requires from 30 to 40 units of insulin daily and the other, from 26 to 32 units.

Late Postoperative Deaths.—Sixteen patients who survived operation have subsequently died. Six patients who were found to have gross carcinoma at the time of operation died in relatively short intervals. Four patients who had an adenoma of the islet cells have since died, and the shortest interval between operation and death in this group was six years. Three of these four patients in whom the adenoma had been removed appeared to be "cured," but in one patient the adenoma was not discovered until autopsy was performed. One patient who had a tumor diagnosed as grade 1 adenocarcinoma remained well for 10 years after operation and then developed a recurrence of symptoms that persisted for one year until the patient died. There was no autopsy. Five patients in whom only normal pancreas was found at operation have since died, the earliest one being two years after operation. All five of these patients evidenced persistence of symptoms, and presumably their death was related to the clinical syndrome they manifested. Autopsy was done on two of these five patients, and no abnormality of the pancreas was found.

SUMMARY AND CONCLUSIONS

Hyperinsulinism is a term reserved for patients who have a hyperfunctioning tumor of the islest of Langerhans or who have received an excessive amount of insulin. It is an uncommon condition. Sugar tolerance curves are of no value in its diagnosis, but fasting from a few hours to 72 hours is of great value. Any patient with true hyperinsulinism should undergo surgical exploration to search for an insulin-producing tumor of the pancreas. Its early recognition and removal may be lifesaving. Our experience in this study is based on 91 patients with hyperinsulinism, in 76 of whom tumors were found. Tumors were not found in some of the remaining 15 patients.

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CLINICAL NOTES

RENAL LESIONS OF SULFONAMIDE TYPE AFTER TREATMENT WITH ACETAZOLAMIDE (DIAMOX)

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and
Edwin R. Fisher, M.D., Pittsburgh

Acetazolamide (Diamox) is widely employed as a diuretic agent. Although it contains a sulfonamide moiety, it differs chemically from all the bacteriostatic sulfonamides in that it does not have a benzene ring. Few side-effects or toxic manifestations have attended its use, but Pearson, Binder, and Neber [1] recently reported a case of agranulocytosis attributable to this drug, and Moseley and Baroody [2] described a hypersensitivity type of reaction to acetazolamide in a patient with known sensitivity to sulfonamide drugs. The nephrotoxic effects of the antibacterial sulfonamides are well known. However, the development of structural renal lesions following administration of acetazolamide has not been noted either in man or in the experimental animal.[3]

The present report describes the occurrence of a nephrotic and hypersensitivity type of renal lesion in a patient who had received acetazolamide. Although the lesions observed were identical with those produced by bacteriostatic sulfonamides, clinical manifestations of

From the medical and laboratory services, Veterans Administration Hospital, and the University of Pittsburgh School of Medicine.

1. Pearson, J. R.; Binder, C. I., and Neber, J.: Agranulocytosis Following Diamox Therapy, J. A. M. A. **157**: 339 (Jan. 22) 1955.

2. Moseley, V., and Baroody, N. B.: Some Observations on the Use of Acetazoleamide ("Diamox") as an Oral Diuretic in Various Edematous States and in Uremia with Hyperkaliemia, Am. Pract. & Digest Treat. **6**: 558 (April) 1955.

3. Gallagher, J. D.: Personal communication to the authors.

renal damage did not occur. The purpose of this communication is to call attention to the renal lesions that developed in this instance, in the hope that it will stimulate closer clinical and morphological studies in patients receiving acetazolamide so that the effects of this drug upon renal structure and the nature of the lesions observed may be better evaluated.

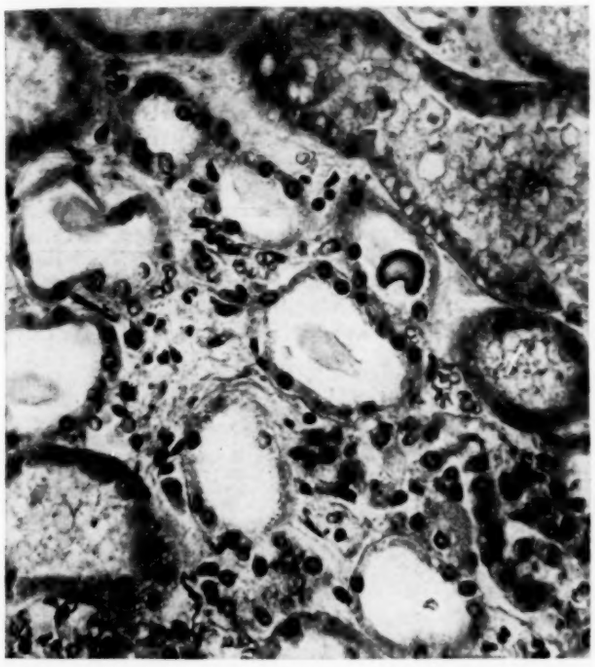

Fig. 1.—Photomicrograph of section of kidney demonstrating crystal in lumen of limb of Henle and marked dilatation of proximal convoluted tubules (×350).

REPORT OF A CASE

A 55-year-old white man developed a mass in his neck in March, 1952. A cervical lymph node removed at biopsy disclosed Hodgkin's disease, granuloma type. Radiation therapy was administered. On Sept. 11, 1954, the patient was admitted to Veterans Administration Hospital, Aspinwall, Pa., complaining of weakness, anorexia, weight loss, abdominal pain, fever, and dyspnea upon exertion. Examination revealed pallor and enlargement of the liver and spleen. The red blood cell count was 2,440,000 per cubic millimeter and the white blood cell count 11,300 per cubic millimeter, and the hemoglobin level was 8 gm. per 100 cc. Study of urine revealed normal findings and a specific gravity of 1.019. Roentgen examination showed the heart to be slightly enlarged. An electrocardiogram disclosed left bundle branch block. Intravenous urography on Sept. 17, 1954, showed normal kidney outlines and good concentration of the contrast medium. Urine specimens during the period of hospitalization were normal with specific gravities ranging from 1.004 to 1.024. A few leukocytes were found in some specimens. Excretion of phenolsulfonphthalein was 55% in two hours. The nonprotein-nitrogen content of the blood was repeatedly found to be within normal limits. The patient was treated with repeated blood transfusions and with various medicaments including cortisone, triethylene melamine, and chlorpromazine. No untoward reaction to the blood transfusions was observed. Peripheral edema appeared and was attributed to cardiac failure; accordingly, the patient was digitalized and mercurial diuretics were administered. Starting on Jan. 4, 1955, the patient received acetazolamide in doses of 250 mg. three times daily for four days. A slight decrease in edema followed. The subsequent clinical course was unaltered. Urinary output exceeded 750 cc. daily except on Jan. 17, 29, and 30, when the urinary outputs measured 510, 300, and 350 cc. respectively. The blood pressure remained normal. The blood nonprotein-nitrogen level, determined on four occasions between Jan. 7 and Jan. 28, ranged from 25 to 40 mg. per 100 cc. The patient's condition gradually deteriorated, and he died on Jan. 31, 1955.

Pathological Findings.—The right kidney weighed 300 gm. and the left 325 gm. Their cortical surfaces were smooth. The capsules stripped with ease, revealing swollen, yellowish-tan cortices. Cut surfaces were also swollen and revealed moderately congested medullas not clearly demarcated from the cortices. The renal pelves and ureters were unobstructed, and their mucosal surfaces were smooth. Microscopically, the proximal convoluted tubules were markedly dilated containing an amorphous, pink-staining coagulum. Their epithelial cells were flattened and contained small cytoplasmic vacuoles that were sudanophilic, indicating their lipid nature. Segments of the loops of Henle contained birefractive crystals within their lumens (fig. 1) as well as proteid casts. The crystals were for the most part spherical or crescent-shaped with radiating striations; rhomboid forms were less frequently present. A greater number of crystals were noted in frozen section preparations, indicating that some of the crystals were rendered soluble by the dehydration and infiltration process inherent in the preparation of paraffin sections. The crystals were morphologically identical with those obtained by recrystallization of acetazolamide from a solution in acidified water. Hemoglobin casts were observed in the lumens of the distal convoluted and collecting tubules; the latter structures also contained crystals. The stroma was edematous and infiltrated with lymphocytes, plasma cells, and a few eosinophils. Focal necrotizing granulomas also were present within the stroma (fig. 2) and were characterized by central zones of necrosis and neutrophils surrounded by histiocytes, lymphocytes, plasma cells, eosinophils, and giant cells of the Langhans type. The glomeruli and arterioles were without significant alteration. Granulomas similar to those noted in the kidney were present in sections of the lung and thyroid gland. Bacterial cultures of this tissue and stains for fungi and acid-fast bacilli were negative. In addition to the renal lesions described, Hodgkin's disease was evident in the cervical, mediastinal, paraaortic, and peripancreatic lymph nodes and the spleen. Severe organizing bronchopneumonia, coronary arteriosclerosis, cardiac dilatation and hypertrophy, and passive congestion of the liver were also present at death.

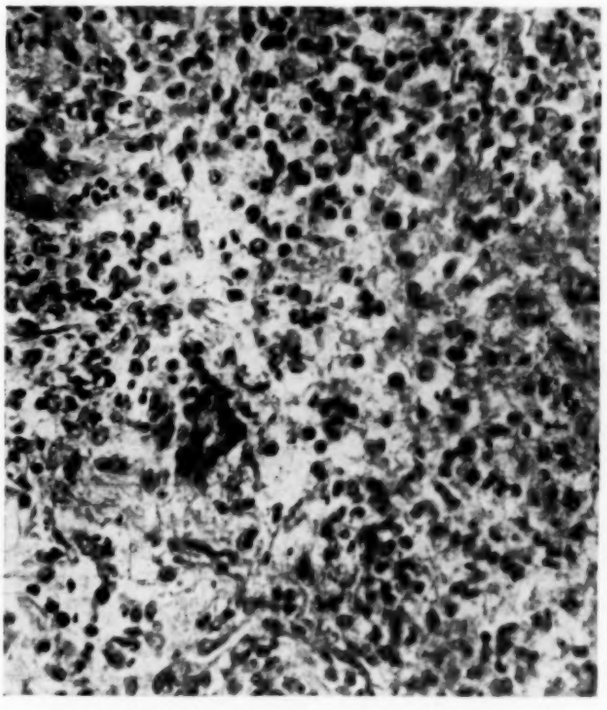

Fig. 2.—Necrotizing granuloma in section of kidney (×150).

COMMENT

In the 24 days that elapsed between the time the patient last received acetazolamide and his death, neither oliguria nor azotemia appeared and urinalysis revealed

no abnormalities. Therefore, the renal changes observed at autopsy probably played no important role in the death of the patient. There was no history of the patient having received any sulfonamide other than acetazolamide, yet the kidney lesions were indistinguishable from those produced by the antibacterial sulfonamides. The crystals in the renal tubules were morphologically similar to the acetylated forms of the bacteriostatic sulfonamides and were identical with crystals obtained from a solution of acetazolamide in acidified water. Although they were not unlike the leucine crystals occasionally observed in the kidneys of patients with hepatic disease, significant alterations were not found in this patient's liver. The granulomatous response observed in the kidneys, lungs, and thyroid has been noted in patients succumbing to sulfonamide intoxication [4]; this lesion is considered to represent an allergic response to the sulfonamide. A similar reaction to acetazolamide may have been experienced by this patient. It is considered possible that renal lesions of the type observed might in some instances be accompanied by clinical manifestations of renal insufficiency.

SUMMARY

A patient with Hodgkin's disease who received acetazolamide (Diamox) for four days showed no clinical evidence of renal failure or sulfonamide intoxication, yet at autopsy 24 days later renal lesions indistinguishable from those produced by the antibacterial sulfonamides were present. Occurrence of renal lesions following the administration of acetazolamide has not heretofore been reported.

Veterans Administration Hospital, University Drive (40) (Dr. Glushien).

4. Allen, A. C.: The Kidney: Medical and Surgical Diseases, New York, Grune & Stratton Inc., 1951. Lederer, M., and Rosenblatt, P.: Death During Sulfathiazole Therapy: Pathologic and Clinical Observations on 4 Cases with Autopsies, J. A. M. A. **119**: 8 (May 2) 1942.

THROMBOCYTOPENIA FOLLOWING ACETAZOLAMIDE (DIAMOX) THERAPY

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While thrombocytopenia is not common following the use of sulfonamide drugs, its occasional occurrence has been well documented. The widespread use of a new sulfonamide derivative, acetazolamide (Diamox), as a diuretic and acid-base regulator might be expected to result in thrombocytopenia in some of its uses. This report describes a case of thrombocytopenic purpura apparently caused by this drug.

REPORT OF A CASE

An 85-year-old white man was admitted to St. Luke's Hospital on March 18, 1954, with purpura and bleeding from the rectum of two days' duration. For years he had suffered from intolerance to fatty foods and intermittent pain in the right upper quadrant. In August, 1946, he had had a cholecystotomy with the removal of 13 gallstones. Postoperatively a biliary fistula developed accompanied by signs of biliary obstruction, which lasted until January, 1947. At this time he was admitted to St. Luke's Hospital for the first time, and cholecystectomy, removal of gallstones, and drainage of the common bile duct were performed on Feb. 7, 1947. Between this time and January, 1954, he had several sporadic episodes of transient biliary obstruction due to cholangitis and gravel in the common bile duct. These were severe enough to necessitate hospitalization in 1949 and 1953 but cleared up without surgical intervention. In 1953 he showed signs of arteriosclerotic heart disease and an electrocardiogram showed an incomplete left bundle-branch block. One month later an electrocardiogram showed, in addition, depression of the S-T segment in leads 1 and V_4, an inverted T wave in lead 1 and diphasic T wave in lead V_4. The patient recovered spontaneously from the episode of bile duct obstruction, but he developed increasing dyspnea and fatiguability and his doctor treated him for congestive failure with digitoxin and diuretics. On Feb. 26, 1954, he commenced taking 250 mg. of acetazolamide three times a day as a diuretic. After a week he noticed some traces of fresh blood in his stools but not enough to cause him concern. On March 16 he had severe bloody diarrhea and developed a generalized petechial skin eruption, most marked on the lower extremities. The bleeding continued, and the patient was readmitted to St. Luke's Hospital on March 18, 1954.

TABLE 1.—*Laboratory Data in Patient with Thrombocytopenia After Acetazolamide (Diamox) Therapy*

Date	Hemoglobin Level, Gm. per 100 Ml.	Red Blood Cell Count ($\times 10^6$), per Cu. Mm.	Platelet Count, per Cu. Mm.
3/19/54	14.5	5.03	4,000
3/22/54	11.0	3.79	11,000
3/23/54	10.2	3.71	11,000
3/24/54	11.0	3.56	9,000
3/27/54	10.8	3.49	13,000
3/29/54	10.5	3.38	15,000
3/31/54	10.2	3.61	6,000
4/ 9/54	10.2	3.64	14,000
4/19/54	11.0	3.48	20,000
4/23/54	11.0	3.96	24,000
5/ 7/54	11.4	4.16	35,000
5/21/54	12.1	4.20	84,000
6/11/54	12.8	4.68	68,000
7/16/54	13.2	4.50	127,000
9/10/54	13.4	4.73	118,000
10/29/54	12.0	4.06	101,000
4/28/55	....	....	350,000

On admission the patient's temperature was 98.6 F (37 C), respirations 20, pulse rate 90 per minute, and blood pressure 190/100 mm. Hg. He was a thin, elderly white man, in no distress, whose skin was covered with petechiae, confluent on the lower extremities. Petechial hemorrhages were also noted on the mucous membranes of the mouth and conjunctiva. The neck veins were prominent, and the heart was enlarged to the left. The chest was emphysematous but clear to auscultation. The abdomen showed the scars of previous operations and was soft and nontender. The liver edge was palpable 3 cm. below the right costal margin; the spleen was not palpable. The prostate gland was twice normal size, firm and nontender. A few external and internal hemorrhoids were present. The legs were covered with petechiae confluent in many areas. There was no edema of the ankles. The blood examination revealed a hemoglobin level of 14.5 gm. per 100 ml., 5,030,000 red blood cells per cubic millimeter, 9,000 white blood cells per cubic millimeter, and 4,000 platelets per cubic millimeter. The differential white blood cell count showed 74% neutrophils, 3% basophils, 19% lymphocytes, and 4% monocytes. The urine contained a trace of albumin and 2 to 10 red blood cells per high-power field. Blood urea was 24.4 mg. per 100 ml., ascorbic acid 1.0 mg. per 100 ml. Prothrombin time was 14.7 seconds (100% prothrombin activity). The stools were grossly bloody on admission and became guaiac negative on March 27, 1954. A sternal marrow specimen aspirated on March 26 showed generalized hyperplasia of all elements. The megakaryocytes were nongranular, and many naked megakaryocyte nuclei were present. Few platelets were seen. The hospital course was uneventful, with prompt subsidence of the gastrointestinal bleeding and gradual clearing of purpura on bed rest.

From the Department of Medicine, St. Luke's Hospital.

Treatment was symptomatic. On March 31 there was a chill, and temperature rise to 100.4 F (38 C), with pains in the upper right quadrant and slight icterus of the scleras, which subsided spontaneously. The platelet count (table 1) remained low until May, 1954, after which it gradually rose to levels above 100,000 per cubic millimeter in July. When the patient was last seen in April, 1955, the platelet count was 350,000 per cubic millimeter and he was free from symptoms.

Special studies to establish the relationship of acetazolamide to the patient's thrombocytopenia were undertaken, and the results are given in table 2. On April 1 a suspension of platelets was prepared from sequestrene-treated blood drawn from normal subjects with siliconized syringes and centrifuged in lusteroid tubes. One milliliter of this suspension containing 600,000 platelets per cubic millimeter was placed in each of four test tubes. To 2 ml. of the patient's citrated plasma was added 1 ml. of a solution containing 0.5 mg. of acetazolamide per millimeter of 3.5% sodium citrate, and in another tube 2 ml. of the patient's plasma was added to 1 ml. of citrate solution alone. Similar preparations were made using the plasma of a normal subject. One milliliter of each mixture was then added to the platelet suspension in one of the four tubes. After 24 hours in the icebox the tubes were thoroughly shaken and platelet counts determined for each tube. The experiment was repeated on April 8 with the patient's plasma alone, using a different suspension of platelets,

TABLE 2.—*Platelet Survival in Plasma With and Without Added Acetazolamide (Diamox)*

Date		Normal Plasma Level, per Cu. Mm.	Normal Plasma Plus Acetazolamide Level, per Cu. Mm.	Patient's Plasma Level, per Cu. Mm.	Patient's Plasma Plus Acetazolamide Level, per Cu. Mm.
4/1/55 after 24 hours		380,000	400,000	250,000	150,000
4/8/55	Initial	.....	.....	243,000	283,000
	After 36 hours	.....	.....	187,000	90,000
5/7/55	Initial	.....	.....	290,000	276,000
	After 24 hours	.....	.....	220,000	170,000

and again on May 6. The platelet count decreased more rapidly in the patient's plasma than in normal plasma. The addition of acetazolamide increased the rate of platelet decrease in the patient's plasma but had no effect on platelet levels in normal plasma.

COMMENT

Prior to his last hospital admission this patient had on two occasions shown some bleeding or bruising tendencies. These, however, were associated with episodes of obstructive jaundice, and when the prothrombin level was measured it was found to be low. On neither of these admissions was there any laboratory evidence of thrombocytopenia; the bleeding tendencies subsided promptly when the jaundice and hypoprothrombinemia were relieved and may justly be attributed to that cause. The bleeding on the last admission, however, is directly attributable to thrombocytopenia. On clinical grounds one could at once suspect acetazolamide (Diamox), which the patient had started to take three weeks before the onset of symptoms, as a causative agent. Acetazolamide is a sulfonamide, a group of drugs known to produce thrombocytopenia on occasion,[1] and has been reported to have induced agranulocytosis.[2]

In purpura caused by Sedormid (allyl-isopropyl-acetyl-carbamide),[3] quinidine,[4] and quinine [5] it has been shown that the drug in question combined with some factor peculiar to the patient's plasma to produce an antiplatelet agglutinin. If a similar mechanism were responsible for this patient's thrombocytopenia it might be demonstrated to be due to acetazolamide by combining his plasma with acetazolamide and normal platelets. In vitro studies of this type indicated that platelets disappeared more rapidly in his plasma in the presence of acetazolamide (table 2) but that acetazolamide did not have this effect when normal plasma was used. No platelet agglutinins were observed in this case; a decrease in platelets was not apparent in the counting chamber during the first hour after mixing.

401 W. 118th St. (27) (Dr. Reisner).

1. Kracke, R. R., and Townsend, E. W.: The Effect of Sulfonamide Drugs on the Blood Platelets, J. A. M. A. **122**: 168 (May 15) 1943.
2. Pearson, J. R.; Binder, C. I., and Neber, J.: Agranulocytosis Following Diamox Therapy, J. A. M. A. **157**: 339 (Jan. 22) 1955.
3. Ackroyd, J. F.: The Pathogenesis of Thrombocytopenic Purpura Due to Hypersensitivity to Sedormid (Allyl-Isopropyl-Acetyl-Carbamide) Clin. Sc. **7**: 249, 1949.
4. Bigelow, F. S., and Desforges, J. F.: Platelet Agglutination by an Abnormal Plasma Factor in Thrombocytopenic Purpura with Quinidine Ingestion, Am. J. M. Sc. **224**: 274, 1952.
5. Steinkamp, R.; Moore, C. V., and Doubek, W. G.: Thrombocytopenic Purpura Caused by Hypersensitivity to Quinine, J. Lab. & Clin. Med. **45**: 18, 1955.

NEW MUSCLE FORCEPS FOR PTOSIS OPERATIONS AND SURGERY OF THE SUPERIOR OBLIQUE

Conrad Berens, M.D., New York

After using a special forceps [1] for surgery of the extraocular muscles, which has proved completely satisfactory for over four years, it was considered desirable to construct a forceps with similar principles for use in ptosis operations. The shaft of the ptosis forceps is 8 cm. in length and 6 mm. in diameter, with a knurled activating screw at one extremity. The jaws at the opposite end of the forceps are 17 mm. in length and 1.5 in breadth (see figure). The lower blade, which has a smooth upper

Muscle forceps for ptosis operations and surgery of the superior oblique.

surface, is perforated to receive the eight teeth located on the lower surface of the upper blade. These teeth, which are 1 mm. in length, serve to grasp the muscle firmly and prevent it from slipping. The upper blade is grooved between the teeth to permit the passage of sutures through the muscle and the grooves in the forceps. The blades can be separated to a distance of 12 mm., which provides adequate space for manipulation of the levator or the superior oblique muscle. The lower blade may be used as a tenotomy hook, to be passed under the muscle to be resected or advanced.

708 Park Ave.

Managing Director, the Ophthalmological Foundation, Inc.

This study was aided by a grant from the Ophthalmological Foundation, Inc., and from the Department of Research, New York Association for the Blind.

The forceps described in this paper are made by Storz Instrument Company, St. Louis.

1. Berens, C.: A New Muscle Forceps, Am. J. Ophth. **34**: 1180 (Aug.) 1951.

COUNCIL ON PHARMACY AND CHEMISTRY

Report of the Council

The Council has authorized publication of the following report.

H. D. KAUTZ, M.D., *Secretary.*

CURRENT STATUS OF THERAPY IN NAUSEA AND VOMITING OF PREGNANCY

At different times in recent years the Council has been requested by pharmaceutical firms to evaluate the use of various drugs for relief of nausea and vomiting of pregnancy. Comparison of the submitted supporting data and the opinions of a panel of Council consultants in obstetrics have disclosed some very interesting differences of opinion concerning the value of drugs other than sedatives in the treatment of this condition.

In one report on an anti-motion-sickness agent it was stated that "nausea and vomiting occurred in almost 80% of all pregnancies," whereas one of the consultants stated, "There have been so few cases of nausea and vomiting of pregnancy that opportunity for study . . . has been limited." Similar contrasting attitudes have been expressed concerning the necessity for active drug therapy. One investigator found it advisable to administer an anti-motion-sickness drug to 182 patients for relief of vomiting of pregnancy; however, a consultant stated, "In the 16 years before 1947 less than one in a thousand obstetrical patients required hospital treatment for this condition, and even fewer since then."

Thus it has become apparent that the wide discrepancy in opinions lies in different interpretations of what is meant by nausea and vomiting of pregnancy. Accordingly, the Council felt it necessary to reconsider the status of drugs used for this purpose on the basis of more precise definition of the terminology. On the recommendation of the American Academy of Obstetrics, a panel of four consultants with experience in this field was polled concerning the terminology as well as the necessity and efficacy of drug therapy.

DEFINITIONS

It was generally agreed by members of the panel that, although the term "nausea and vomiting of pregnancy" is applicable to both mild and severe forms, its use should be restricted to the condition, commonly observed during the first 14 or 16 weeks of pregnancy, that is characterized by some disturbance in appetite and reactions to food in a fairly large percentage of women. These reactions may vary from morning nausea to occasional emesis but are not accompanied by any signs of disturbed nutritional status. The percentage of women so affected, if detailed inquiry is made of all patients, was estimated to be 25 to 30% or slightly more, but in most instances the symptoms are so mild that the patient overlooks them.

1. King, A. G.: The Treatment of Pregnancy Nausea with a Pill, Obst. & Gynec. 6: 332-338 (Sept.) 1955.

It was also agreed that in most of the more severe cases there were some elements of underlying emotional disturbance.

The panel felt that the term hyperemesis gravidarum, or pernicious vomiting of pregnancy, should be applied to the condition occurring in the few patients who exhibit intractable vomiting and signs of disturbed nutritional status, such as alteration of electrolyte balance, 5% or more weight loss, ketosis, and acetonuria, with ultimate neurological disturbances, liver damage, retinal hemorrhage, and renal damage. One member of the panel felt that ketosis and acetonuria should not be regarded as critical evidence of hyperemesis. This serious pathological condition apparently occurs only rarely in pregnant women who have proper early prenatal care and protection from serious emotional disturbances. In the experience of the consultants, most patients with hyperemesis gravidarum were under mental stress suggested by or related to the pregnancy.

ETIOLOGY

In attempting to evaluate the need and value of drugs, the lack of definitive knowledge concerning the cause of the emesis of pregnancy is a limiting factor; however, there is agreement on at least two points of etiological responsibility—pregnancy and psychological factors.

Pregnancy apparently predisposes many women to gastrointestinal disturbance. Since these symptoms and signs seldom persist after the trophoblast is fully formed (16 weeks), it has been assumed that an unusual hormonal stimulus exists during the early phases of pregnancy. Treatment with estrogen and progesterone, however, has not been successful in alleviating the situation. Another assumption has been that the conceptus is producing some toxic substance during the first trimester, but no adequate support for this theory has been demonstrated.

There is little question that psychological factors play a major role in both mild and severe nausea and vomiting of pregnancy. This has often been offered as the explanation for the beneficial results reported after psychotherapy, painful procedures, administration of placebos, and the use of various unrelated drugs.[1] Psychiatrists state that strong dependent needs for relief or escape from the ordinary stresses of daily existence are usually present in the patient. When the additional burden of pregnancy occurs, it produces a violent and often subconscious rejection of this increased demand on the patient's already overburdened life situation. The resultant psychomotor pressures are manifested through the visceromotor nervous system.

DIAGNOSIS AS A GUIDE TO TREATMENT

In all instances of nausea and vomiting associated with pregnancy a complete examination should be performed to rule out any possible cause other than the pregnancy. If the diagnosis seems to be the more or less physiological nausea and vomiting of pregnancy as previously described, in the opinion of the panel general instructions will ordinarily suffice, such as adequate rest, lightening of household burdens, avoidance of nervous excitement, and ingestion of frequent small meals high in carbohy-

drate content. The patient should be repeatedly reassured that her condition is not serious and is self-limited; she should also be encouraged by the physician to discuss any problem and fear associated with her pregnancy. If sedation is required, 60-100 mg. of phenobarbital or a similar barbiturate may be given twice daily. Because of the emotional factors involved, it is not surprising to find that psychotherapeutic techniques are frequently successful and that placebos are often as effective as test drugs in blind studies. Since mild forms of nausea and vomiting may flare into the intractable form suddenly and without warning, patients should be kept under close observation until the symptoms subside (seldom later than the 16th week of pregnancy).

Hyperemesis gravidarum, on the other hand, requires immediate active therapy to overcome the effects of disturbed nutrition by means of parenterally given alimentation, readjustment of electrolyte balance, and vitamin replacement. These measures plus hospitalization, quiet surroundings, sedation, and reassurance may be sufficient to break the cycle of vomiting.

DRUG THERAPY

One of the members of the panel concluded that valid methods for the clinical investigation of proposed drugs for treatment should include blind or double-blind studies, because the symptoms are self-limited and spontaneously of great variability in intensity, and also because the psychic component involved in both morning sickness and hyperemesis gravidarum is so great. When such methods of investigation were employed, most of the drugs tested had about the same level of effectiveness as a placebo.[2]

In reviewing the drugs that are currently employed in the alleviation of the symptoms of nausea and vomiting associated with pregnancy, the following categories may be found: (1) antihistaminics and the related anti-motion-sickness drugs, (2) anticholinergics, (3) vitamins, and (4) depressants.

The antihistaminic and anti-motion-sickness drugs in blind studies appear to be no more effective in simple nausea and vomiting of pregnancy than placebos.[2] It is doubtful whether they are of value in the treatment of hyperemesis gravidarum. Any effect obtained with their use can be attributed to a sedative action rather than to any specific inhibition of nausea or vomiting. The Council was informed of a study in progress by the blind test technique on one of the anticholinergic drugs that may be helpful in determining the possible usefulness of agents that inhibit gastrointestinal motility. Most vitamins appear to be of value only as replacements for deficiencies induced by hyperemesis gravidarum and are no more effective than placebos in simple nausea and vomiting of pregnancy[2a]; however, since pernicious vomiting is frequently characterized by a specific deficiency of pyridoxine (vitamin B_6), administration of this vitamin may be of value, in some cases, in the treatment of hyperemesis gravidarum.

The depressant chlorpromazine has shown considerable promise in the treatment of hyperemesis gravidarum.[3] Although a blind study has not been performed, chlorpromazine has been reported to cause complete or almost complete cessation of symptoms in hyperemesis gravidarum in one to five days.[2c] Such patients should be carefully followed for evidence of blood or liver damage. Since chlorpromazine may induce serious side-effects, it probably should not be employed in physiological nausea and vomiting of the first trimester and should be reserved for trial in pernicious vomiting, preferably before hepatic damage has occurred.

SUMMARY

Nausea and vomiting of pregnancy may be characterized as either physiological or pernicious. As a guide to management, it is important to distinguish between these two types and nausea due to causes other than pregnancy. The common physiological form usually responds to simple dietary measures, mild sedation, and psychotherapy; the rare pernicious type requires sedation as well as active hospital treatment to restore electrolyte balance and replace caloric and vitamin losses. Various drugs, including most vitamins, antihistaminics, and anti-motion-sickness drugs, have not been demonstrated to exert a more specific effect than placebos or sedatives upon either form of nausea and vomiting associated with pregnancy. Double-blind studies with a placebo and a sedative should be employed in the further clinical investigation of drugs proposed for this purpose. In some cases, vitamin B_6 (pyridoxine) may be of value as an adjunct in the treatment of pernicious vomiting of pregnancy. Meanwhile, chlorpromazine is considered to be a sufficiently active antiemetic to warrant a trial in the pernicious form of vomiting of pregnancy, preferably before damage to the liver has occurred.

2. (*a*) Dill, L. V.: Vomiting Associated with Pregnancy, M. Ann. District of Columbia **18**: 178-184 (April) 1949. (*b*) Cartwright, E. W.: Dramamine in Nausea and Vomiting of Pregnancy, West. J. Surg. **59**: 216-234 (May) 1951.

3. (*a*) Kent, B., and others: Clinical Observations on the Use of Chlorpromazine (SKF-2601A) as an Antiemetic Agent, M. Rec. & Ann. **48**: 758-761 (Jan.) 1954. (*b*) Moyer, J. H., and others: Clinical Studies of an Anti-Emetic Agent, Chlorpromazine, Am. J. M. Sc. **228**: 174-189 (Aug.) 1954. (*c*) Benarson, H. B., and others: The Use of Chlorpromazine in the Obstetric Patient: A Preliminary Report, Am. J. Obst. & Gynec. **69**: 776-779 (April) 1955.

Effect of Reserpine in the Newborn.—Reserpine has a definite effect in the newborn infant of mothers who received it prior to delivery. There was a total of 77 mothers who received reserpine alone or in combination with other drugs. . . . Sixteen percent of the infants of these mothers had toxic symptoms, while the mothers themselves showed no reactions. Furthermore, several infants, including twins, since that time have demonstrated nasal discharge, and on investigation it was found that reserpine had been administered to the mothers prior to delivery. It appears therefore that this is either a sensitivity peculiar to the newborn or that it is due to rapid accumulation of the drug in the infant via the placenta. All these mothers received the drug within two days of delivery. There does not appear to be any correlation between amount administered, time of onset, and severity of symptoms. Microscopic examination of the lungs of the two patients who died showed alveoli containing desquamated epithelial cells, erythrocytes, and some protein material. This did not appear to be principally inflammatory, nor were there findings of hyaline-membrane disease or simple aspiration. There also appears to be a generalized vascular dilatation of the capillaries and venules which may be a secondary effect of anoxia, a result of the drug alone, or a result of both these factors.—I. S. Budnick, M.D., S. Leiken, M.D., and L. E. Hoeck, M.D., Effect in the Newborn Infant of Reserpine Administered Ante Partum, *A. M. A. American Journal of the Diseases of Children*, September, 1955.

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COMMONWEALTH FUND AND FORD FOUNDATION SUPPORT MEDICAL EDUCATION

Announcement of the recent commitments of the Commonwealth Fund and the Ford Foundation in support of medical education has been generally received with acclamation and sincere public appreciation. Ten university medical schools have received grants totaling $7,150,000 for medical education from the Commonwealth Fund. The Ford Foundation will grant 90 million dollars to privately supported medical schools as endowment to help them strengthen their instruction, although the exact allocation to the individual schools has not yet been determined. These two great philanthropic organizations have recognized that, unless the increasing financial needs of medical education are met, the current high standards of medical training in the United States are in jeopardy. These grants will aid in meeting some of the needs that have existed during recent years, but they have not closed the gap that has been represented as being equivalent to approximately 10 million dollars annually for all needs. In other words, there is still great need for active and increasing support of medical education through the American Medical Education Foundation and the National Fund for Medical Education if the estimated current needs are to be adequately covered.

There is need of more general appreciation of the fact that the present-day medical school is no longer simply an educational institution devoted solely to the undergraduate training of physicians. Today's medical schools are complex centers of medical science, concerned with the basic education of medical students, with the provision of graduate and postgraduate education for physicians, and with the conduct of activities in the constant search for new knowledge and in the prevention, diagnosis, and treatment of human illness.

The growth of medical school responsibilities has been a natural accompaniment of the rapidly accumulating advances in scientific knowledge applicable to medicine. In this dynamic period no school of medicine can exist as an isolated teaching entity solely concerned with undergraduate medical education and disinterested in the increasing demand for continuing education, the search for new knowledge, or its application in the prevention, diagnosis, or treatment of human problems. Every possible effort should be made to obtain the additional financial backing necessary to maintain and further develop the needs of our medical schools. The Commonwealth Fund and the Ford Foundation have given a vital "shot in the arm" in support of these needs. Their evidence of concern for and support of medical education should serve as a stimulus to other foundations, to industry in general, and to all members of the profession to redouble efforts to achieve the over-all financial needs of our medical schools, so that their continued progress may be assured.

URINARY INFECTIONS

According to Cook,[1] infections of the urinary tract are in general poorly treated. It is important to determine first whether an infection of the urinary tract is actually present and if so whether it is an uncomplicated infection or is secondary to some coexisting lesion such as calculus, tumor, obstruction, or scar. If such a secondary lesion exists, treatment directed primarily at the infection will not cure the condition.

Acute cystitis is the commonest of the urinary tract infections, and about 80% of such infections are caused by gram-negative bacilli.[2] For this reason it is well to make a gram stain of the sediment obtained by centrifuging a specimen of the patient's urine collected under sterile conditions. Efforts to avoid introducing contaminants cannot be overemphasized, because many unfortunate patients with no infection have been treated for cystitis when the organisms found (usually Proteus organisms, Streptococcus faecalis, or Pseudomonas organisms) were contaminants. If no micro-organisms are seen under the microscope, viral infection must be considered. A complete diagnostic study is indicated if a coexisting lesion is suspected, especially if two or three courses of treatment have not cleared up the infection.

Although a plethora of new chemotherapeutic agents have been recommended for the treatment of urinary infections, a sulfonamide or combination of sulfonamides should be tried first. If this fails, as it does in about 10% of these patients, nitrofurantoin or one of the tetracyclines may be used. Sensitivity studies should not be made routinely because they are time-consuming, expensive, and often of little value. If, however, two or three courses of treatment have not cured the infection, such studies may be indicated. For infections caused by Streptococcus hemolyticus, penicillin is usually best; for those caused by S. faecalis, if the organism is resistant to sulfonamides and penicillin, nitrofurantoin should be tried; for those caused by Neisseria gonorrhoeae, penicillin may be combined with a sulfonamide; for those caused by Micrococcus pyogenes, since most strains are now resistant to penicillin, a sulfonamide or erythromycin is best; and for those caused by a mixture of bacilli

1. Cook, E. N.: The Management of Infections of the Urinary Tract, Ann. Int. Med. **43**: 316-322 (Aug.) 1955.
2. Collier, E. J., and others: Urologic Problems in General Practice, Rocky Mountain M. J. **51**: 888-896 (Oct.) 1954.

and cocci, a combination of sulfonamide with penicillin or erythromycin should be given. It is a mistake, however, to treat chronic prostatitis or epididymitis with antibiotics or to try to clear up an asymptomatic pyuria in a patient who has had a prostatectomy. Trafton [3] reports that carbomycin is effective against gram-positive organisms, especially S. faecalis, in the urinary tract. It has a low toxicity but in some patients may enhance the growth of gram-negative organisms.

In the treatment of urinary tract infections, such sulfonamides as sulfadiazine, phthalylsulfathiazole, and sulfamerizine have definite place, as they are effective against a wide variety of organisms and have few side-effects.[4] Every antibiotic used is ineffective against some of the organisms that cause urinary infections, and sulfonamides are less likely than antibiotics to cause the development of drug-resistant organisms. Sulfonamides are also cheaper. Unless there is some contraindication to the use of sulfonamides, they should be tried first, and, if they do not cure the infection, instead of changing to therapy with antibiotics, a search should be made for the underlying cause.

DERMATOPHYTOSIS OF THE FEET

Although dermatophytosis of the feet is usually a minor health problem, it is widespread and at times causes great discomfort and even disability. The causative organism may be found widely dispersed in the environment. It has been difficult to recover from floors, but Ajello and Getz [1] have succeeded in doing so. Shoes and socks also harbor the organisms, and they can be removed therefrom only with great difficulty. Broughton [2] found that pathogenic fungi were readily recovered from the socks of patients with this disease even after laundering. He learned further that these fungi can survive for at least five months in laundered but unworn socks and then grow under moist conditions, without the aid of any medium other than the fabric and any retained cutaneous scales that might be present. Dyed cutaneous scales were traced through six launderings of woolen socks, but only two launderings of thick broad-mesh nylon (as contrasted with spun reinforced nylon) socks. In commenting on Ajello's recovery of pathogenic fungi from shoes, Sulzberger stated that he believed that, had the observers examined the feet of the wearers of the shoes, the yield would have been even greater. Baer and his co-workers [3] were able to recover pathogenic fungi from the sterile water in which the feet of some patients with fungous disease were immersed for 15 minutes and from a smaller but definite proportion of persons with no skin lesions. In spite of the undoubted prevalence of these organisms in the surroundings, intimate family contact has not been commonly observed as a means of spread of the disease.

A controversy has arisen as to whether new lesions appearing after the skin has been cleared of the disease are due to reinfection from an exogenous source, e. g., floors, shoes, socks, or towels, or are due to sudden growth of organisms remaining in the skin and favored by a lowering of local resistance. It is important to resolve this controversy because, if the latter is the case, such measures as the exclusion of persons with fungous disease from public swimming pools, the use of disinfectants on the floors and disinfectant foot baths in showers and locker rooms, and the wearing of disposable slippers would be of no avail. Evidence to support such a view is increasing. Experimental transmission of the disease from one person to another has been successful only when the inoculated skin has been thoroughly macerated and kept so for several days after inoculation. Such conditions could not account for the natural occurrence of the disease. Baer [3] had 14 volunteers expose one foot for 30 minutes in a foot bath in which a patient with active dermatophytosis had soaked his feet. This water contained at least three pathogenic fungi per cubic centimeter. Another 31 subjects soaked one foot in water to which viable fungi from cultures were added. This water contained up to 260 organisms per cubic centimeter, or a much greater concentration than would be met under ordinary conditions of accidental exposure. None of the volunteers acquired active fungous infection, and 18 failed to show fungi in their skin scrapings at any time in a six-week period of observation. In the rest fungi were found in one or more scrapings, and in 15 of these fungi were found in scrapings from the unexposed or control foot. Further studies by the same group (this issue, page 184) confirm their earliest findings.

Sulzberger states that all attempts to sterilize either shoes or feet routinely have been disappointing and have indeed caused skin irritations that were more severe than the usual manifestations of dermatophytosis. To be realistic, control measures should be based on the findings described. Granted that fungi are shed in water and on floors by most patients with dermatophytosis, they may also be shed by persons with no evidence of active infection and, like the ubiquitous Micrococcus (Staphylococcus) organisms, they may be carried on the skin of most persons without causing disease. Many now assume the conclusion to be drawn from recent observations is that contact in itself plays a minor role in producing fungal lesions and that the main cause is a lowering of local resistance in certain areas of the skin. They also believe this local resistance is best maintained by keeping the skin of the feet dry through the use of perforated shoes, especially in summer, the use of a drying powder that is mildly fungicidal in the shoes, the use of a nonalkaline detergent for the feet by persons who are highly susceptible to infection, and the wearing of socks made of absorbent fabrics such as cotton, wool, and thick broad-mesh nylon rather than rayon or spun nylon.

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3. Trafton, H. M., and Lind, H. E.: Carbomycin in the Treatment of Enterococcal Urinary Tract Infections, Antibiotics & Chemother. **4**: 43-47 (Jan.) 1954.

4. Everett, H. S., and Long, J. H.: The Treatment of Urinary Infections, Am. J. Obst. & Gynec. **67**: 916-930 (April) 1954.

1. Ajello, L., and Getz, M. E.: Recovery of Dermatophytes from Shoes and Shower Stalls, J. Invest. Dermat. **22**: 17 (Jan.) 1954.

2. Broughton, R. H.: Reinfection from Socks and Shoes in Tinea Pedis, Brit. J. Dermat. **67**: 249 (July) 1955.

3. Baer, R. L.; Rosenthal, S. A.; Rogachefsky, H., and Litt, J. Z.: Newer Studies on the Epidemiology of Fungous Infections of the Feet, Am. J. Pub. Health **45**: 784 (June) 1955.

COUNCIL ON MEDICAL EDUCATION AND HOSPITALS

SUPPLEMENTARY LIST—CORRECTIONS

INTERNSHIP AND RESIDENCY NUMBER

In the annual Internship and Residency Number of THE JOURNAL, Sept. 24, 1955, the data on a number of services were incompletely or inaccurately presented. The corrected entries for these services are as follows:

APPROVED RESIDENCIES AND FELLOWSHIPS

(beginning on page 291)

ANESTHESIOLOGY

	Chief of Service	Total Anesthetics	Inhalation Anesthetics	First Year Residencies Offered [8]	Total Residencies Offered [8]	Beginning Stipend (Month)
Kings County Hospital Brooklyn, N. Y.	.....	10,925	6,718	..	..	$104
Maimonides Hospital Brooklyn, N. Y.	.....	.....	.....	..	..	...
Albert Einstein Medical Center, Northern Division, Philadelphia	M. L. Bernsteine	8,463	7,372	3	6	200
University of Utah Affiliated Hospitals Salt Lake City						
Salt Lake General Hospital, Salt Lake City	C. M. Ballinger	1,998	1,570	2	3	175
Holy Cross Hospital Salt Lake City	P. A. Clayton	5,900	4,613	1	2	200
St. Marks Hospital Salt Lake City	H. O. Brown	5,716	4,714	..	1	225
Veterans Administration Hospital, Salt Lake City	C. J. Metcalf	873	457	1	2	236
Veterans Administration Hospital, (Fort Douglas) Salt Lake City	H. R. Mershon	171	93	..	..	...

DERMATOLOGY AND SYPHILOLOGY

Kings County Hospital, Brooklyn N. Y. — C. Chiaramonte, Chief of Service; Inpatients treated: 399; Outpatient visits: 7,052; Beginning Stipend: 104

GASTROENTEROLOGY

University of California Hospital, San Francisco — Length of Approved Program (Years): 1

INTERNAL MEDICINE

	Chief of Service	Inpatients Treated	Autopsies	First Year Residencies Offered [8]	Total Residencies Offered [8]	Length of Approved Program (Years)	Beginning Stipend (Month)
Jewish Chronic Disease Hospital, Brooklyn, N. Y.	M. G. Goldner	1,373	14	10	22	3	$175
Jewish Hospital, Brooklyn, N. Y.	E. L. Slevin	2,251	100	4	8	3	75
Kings County Hospital County Division, Brooklyn, N. Y.	.....	5,833	213	..	..	..	104
University of Oregon Medical School Hospital and Clinics, Portland, Ore.	.....	.....	...	..	..	3	...

INTERNAL MEDICINE—Continued

	Chief of Service	Inpatients Treated	Autopsies	First Year Residencies Offered [8]	Total Residencies Offered [8]	Length of Approved Program (Years)	Beginning Stipend (Month)
Episcopal Hospital, Philadelphia	S. R. Vogel	1,955	116	1	3	3	150
Methodist Episcopal Hospital, Philadelphia	H. F. Robertson	3,115	81	..	3	1	200
Veterans Administration Hospital, Richmond, Va.	W. T. Thompson, Jr.	4,985	110	9	27	3	...

NEUROLOGICAL SURGERY

	Chief of Service	Inpatients Treated	Autopsies	First Year Residencies Offered [8]	Total Residencies Offered [8]	Length of Approved Program (Years)	Beginning Stipend (Month)
Northwestern University Medical Center	.....	....	..	..	..	3	...
Chicago Wesley Memorial Hospital,[1-3] Chicago	P. C. Bucy	71	4	..	3	3	50
Passavant Memorial Hospital,[1-3] Chicago	L. Davis	166	1	1	3	..	50
Veterans Admin. Research Hospital, Chicago	L. Davis	26	3	2	5	..	...
Evanston Hospital, Evanston, Ill.	J. Tarkington.	90	3	1	1	..	50

OPHTHALMOLOGY

Massachusetts Eye and Ear Infirmary, Boston — Beginning Stipend (Month): 41

ORTHOPEDIC SURGERY

Kings County Hospital
- County Division, Brooklyn, N. Y. — Inpatients Treated: 426
- University Service, Brooklyn, N. Y. — Inpatients Treated: 287

OTOLARYNGOLOGY

	Chief of Service	Inpatients Treated	Outpatient Visits	First Year Residencies Offered [8]	Total Residencies Offered [8]	Beginning Stipend (Month)
Charity Hospital of Louisiana						
Louisiana State University Unit, New Orleans	V. H. Fuchs	639	8,049	1	3	$100
Tulane University Unit, New Orleans	J. W. McLaurin.	634	7,759	1	3	100
Massachusetts Eye & Ear Infirmary, Boston	.....	.....	.....	..	..	41
Kings County Hospital						
County Division, Brooklyn, N. Y.	.....	441	4,709	..	..	104

PATHOLOGY

	Chief of Service	Number of Autopsies	Number of Surgical Specimens	Number Examined Microscopically	Total Number of Laboratory Examinations	Length of Approved Program (Years)	Beginning Stipend (Month)
Salem Hospital, Salem, Mass.	.....	282	...	...	.....	...	....
Bishop Clarkson Memorial Hospital, Omaha	.....	111	...	...	97,153	...	....
Kings County Hospital, Brooklyn, N. Y.	.....	1,156	13,744	12,962	718,821	...	$104
Dr. W. H. Groves Latter-Day Saints Hospital, Salt Lake City	.....	...	...	...	.....	3[9]	....

PEDIATRICS

	Chief of Service	Inpatients Treated	Autopsies	First Year Residencies Offered [a]	Total Residencies Offered [a]	Length of Approved Program (Years)	Beginning Stipend (Month)
Children's Medical Center, Dallas, Texas	.....	.....	..	..	..	..	$130
Kings County Hospital County Service, Brooklyn, N. Y.	I. Mullin.....	3,371	34	4	6	2	104

PHYSICAL MEDICINE

	Chief of Service	Inpatients Treated	Number of Treatments	First Year Residencies Offered [a]	Total Residencies Offered [a]	Length of Approved Program (Years)
Veterans Administration Hospital, Boston (Jamaica Plains)	F. Friedland.....	1,800	110,000	1	3	1
Veterans Administration Hospital, Cleveland	.....	.....	.....	..	..	2
Veterans Administration Hospital, Oklahoma City	.....	.....	.....	..	..	3
Veterans Administration Hospital, Philadelphia	.....	.....	.....	..	..	3
University of Kansas Medical Center, Kansas City, Kan.	.....	.....	.....	..	..	3
Veterans Administration Hospital, Houston, Texas	.....	.....	.....	..	..	3

PLASTIC SURGERY

Kings County Hospital County Division, Brooklyn, N. Y.	Inpatients Treated: 827; Autopsies: 7; Beginning Stipend (Month): 104

RADIOLOGY

Veterans Administration Hospital, St. Louis	Length of Approved Program (Years): 2
Kings County Hospital, Brooklyn, N. Y.	Number of Superficial X-Ray Treatments: 1,698

SURGERY

	Chief of Service	Inpatients Treated	Autopsies	First Year Residencies Offered [a]	Total Residencies Offered [a]	Length of Approved Program (Years)	Beginning Stipend (Month)
Santa Barbara Cottage Hospital, Santa Barbara, Calif.	H. V. Findlay	1,019	10	4	9	4	$140
Indiana University Medical Center Hospitals Indiana University Med. Center, Indianapolis	H. B. Shumacher, Jr.	1,188	50	5	14	4	165
Veterans Administration Hospital, Indianapolis	J. C. Finnernan	1,166	27	2	5	4	...
Roosevelt Hospital, New York	J. E. Thompson	(Omitted)					
Sacred Heart Hospital, Spokane, Wash.	.....	.....	..	..	..	1-2 Prespecialty training	

UROLOGY

Kings County Hospital University Service, Brooklyn, N. Y.	Length of Approved Program (Years): 3

BUREAU OF MEDICAL ECONOMIC RESEARCH

ILLNESSES TREATED BY PHYSICIANS

Frank G. Dickinson, Ph.D.

A recent book, "Why Patients See Doctors," by Seymour Standish Jr., Blair M. Bennett, Kathleen White, and L. E. Powers, M.D. (Seattle, University of Washington Press, 1955) should be of much interest to physicians. The results of the 1953 Washington Sickness Survey, a statewide study of the incidence of illness as seen by physicians in private practice, are summarized in this concise monograph. Wishing to discern the leading causes of illness in the state, the Washington State Health Council initiated and undertook the project with the cooperation of physicians and health organizations. The title "Why Patients See Doctors" is somewhat misleading; this study does not examine the motivations of the patient but is concerned with the physician's diagnosis only. The objective was to determine "if the major efforts in disease prevention and detection were being spent in the most important areas." Relatively complete mortality data are now available, but few morbidity data are available either for the country as a whole or for the separate states. Some studies have been done for selected groups; i. e., prepaid hospitalization subscribers, but these have obvious limitations. The results of this first comprehensive statewide study of medically attended illness should provoke widespread interest.

A comparison of the principal causes of illness with the leading causes of death in 1953 gives a new perspective on the health problems of the population. For example, cardiovascular diseases rank first as a cause of death in Washington (41.8% of all deaths in 1953) but only fourth in diagnoses reported (7.7% of all visits). Neoplasms rank 2nd as cause of death, but only rank 11th in diagnoses reported.

This study was limited to medically attended illness—those patients seen by physicians in active private practice. Pretested questionnaires were sent to all physicians and osteopaths. The doctors were asked to list all patients seen from midnight to midnight on four selected Tuesdays (Tuesday was considered a typical practice day) spaced at three-month intervals to account for seasonal variation. The simple questionnaire asked only for age and sex of the patient, his chief complaint, and the diagnosis. An average of one-third of the doctors responded, and a total of 73,188 patient visits are recorded. A projection of these figures would give an average of five visits per year for each Washington resident.

In Washington state, 42.2% of physicians in private practice were general practitioners; they attended 56% of the patients and accounted for 47.1% of the survey returns. Specialists, part time and full time, totaled 52.8% of the physicians; they saw 38% of the patients and returned 46.7% of the questionnaires. Osteopaths, who are licensed to use all the healing methods and drugs

available to physicians, numbered 5% of all doctors; they attended 6% of the patients and returned 6.2% of the questionnaires.

Diagnoses are classified in broad illness categories and by subcategories according to the International List.[1] Fifty-four tables and charts are presented throughout the text. The results of these tabulations give some insight into the burden of illness, at least as it affected the population on four specific days of 1953.

HIGHLIGHTS OF THE STUDY

The broad field of health supervision accounted for the largest number of patient visits—16.2%. Health supervision as a category included all prenatal and postnatal visits, well-baby care, immunizations, after-care following medical or surgical attention, examinations, and all visits in which no illness was found. As would be expected, most of this care was given by general practitioners, obstetricians, and pediatricians. Excluding those visits occasioned by pregnancy and the supervision of the first year of life, preventive medicine as such actually accounted for less than 6% of all visits and was a small proportion of medical practice.

The most frequently seen illnesses, according to the survey, were the respiratory diseases, including influenza, pneumonia, bronchitis, and the acute upper respiratory infections; these accounted for 11.9% of all patients' visits. General practitioners attended over 71% of the cases, which were prevalent throughout the year. Respiratory diseases were relatively important, although less so at the upper ages. Accident cases comprised a substantial portion of medical practice in Washington, accounting for about 10% of the visits. Patients under age 5 and over age 65 had proportionately fewer accidents than the other age groups, and, except after age 65, males far outnumbered females as accident victims. Most of these accidents were preventable, and the authors suggest that the current emphasis on accident prevention is quite appropriate.

Although cardiovascular diseases ranked 12th (3.5% of patients) in age group 25-44, with advancing age these diseases became increasingly important and ranked first in all age groups over 45. General practitioners attended about 60% of patients with this diagnosis. In only 3% of patients was mental illness the primary diagnosis.

Although the age-sex distribution of the general practitioner's patients followed that of all patients in the survey, each specialty varied considerably in this respect. Tables are given that show the most common diagnoses, plus the age-sex distribution for each type of practice. The practice of osteopaths shows little similarity to that of medical practitioners, either in the age-sex distribution of patients or in the diagnoses reported. Although the osteopath's training supposedly fits him to serve as a "family doctor," the study shows his practice to be somewhat more limited than is his claim. Most of his patients were concentrated in the 25-64 year age groups, with the young and the old forming a smaller proportion of his practice. More women than men consulted him, but he did very little obstetrics. Accidents accounted for 23.6% of visits to the osteopath, three-fourths of these being for strains and sprains (which are classified as accidents by the International List). Arthritic and rheumatic patients constitute a large part of his practice.

A comparison is made of the differences in diagnoses reported by general practitioners in the rural and small town areas and those in the urban areas; in spite of the rural physician's frequent lack of "adequate diagnostic facilities," there is virtually no statistical difference. The returns were also compared for seasonal variations; the only major difference found was that respiratory illnesses were at a height in January, ranked second in April and October, and ranked third in July. Other variations were minor.

In all age groups over age 15, women outnumbered men as patients. In age group 15-24, women patients were twice as numerous; this is partly because of the large number of prenatal and postnatal visits. Even excluding all visits for pregnancy, female patients still outnumbered males. This is interesting in light of the findings reported in "Age and Sex Distribution of Hospital Patients," [2] which indicated that an excess of males over females was actually hospitalized on the day of reporting in 1953. A cursory comparison is made with other recent morbidity studies, although none of them is strictly comparable. It should be pointed out that the information presented in this book is a summary; more detailed breakdowns of the data are available from the Washington State Health Council in Seattle.

COMMENT

Considerable difficulty surrounds any attempt to assess the incidence of illness for the whole population; the Washington Sickness Survey is no exception. Because of the simplicity deemed necessary in the questionnaire, desirable information was omitted. Only principal diagnosis was tabulated, with no consideration of multiple diagnoses. Place of visit (office, hospital, or home) and whether the visit was the first or a repeat visit were not designated, nor was the individual doctor or patient participation specifically recorded. Of course, no information is available for the nonrespondent physician population, nor is there knowledge of respondent physicians' practices on other than the survey dates. These qualifications on reliability of the study are, nevertheless, adequately described. Even with its limitations, the study should prove interesting to those concerned with the incidence of illness.

Disease prevention programs can scarcely be undertaken in all fields with equal vigor, so a comprehensive view of illness is necessary for the most effective utilization of research and educational facilities. The results of this survey may well serve as a guide in the planning of undergraduate and postgraduate education, as well as focusing attention on the most significant health problems of the state. The authors also express the hope that groups in other states will be stimulated to undertake similar studies. Physicians and vital statisticians share that hope.

1. International Statistical Classification of Diseases, Injuries and Causes of Death, revision 6, Geneva, Switzerland, World Health Organization, 1948.

2. Dickinson, F. G.: Age and Sex Distribution of Hospital Patients, Bulletin 97, Bureau of Medical Economic Research, Chicago, American Medical Association, 1955.

MEDICAL NEWS

ARIZONA

Course on Lip Reading.—The Arizona Society for Crippled Children and Adults, 207 Arizona Title Building, Phoenix, which is conducting a 10-week course on lip reading for adults on Monday evenings, 7-8 p. m., announces that its second course will start in February. All adults with hearing problems are welcome to apply for enrollment for the course. A physician's recommendation and hearing test are prerequisite to enrollment. The fees paid will be determined on a sliding scale based on ability to pay. No one will be ineligible for the class because of financial reasons.

Cancer Seminar Program.—The Arizona division, American Cancer Society, will present the Cancer Seminar program for 1956 at Paradise Inn, Phoenix, Jan. 26-28. Topics for discussion include: neoplasms of the thyroid gland and of the liver and pancreas; cancer of the stomach and of the skin; psychiatric aspects of malignant diseases; and tumors of the spinal cord. A clinicopathological seminar on neoplasms of the lung is scheduled for Friday afternoon. The seminar speakers will be: Dr. Juan del Regato, Colorado Springs, Colo.; Drs. Herbert C. Maier, Alexander Brunschwig, Alfred A. Gellhorn, and Brewster S. Miller, New York City; Drs. Ian G. Macdonald and Rupert B. Raney, Los Angeles; Dr. Averill A. Liebow, New Haven, Conn.; Dr. Leo G. Rigler, Minneapolis; Dr. C. H. Hardin Branch, Salt Lake City; and Dr. David A. Wood, San Francisco.

CALIFORNIA

Course on Pediatric Dermatology.—Stanford University School of Medicine, Stanford University-San Francisco, will present a course in practical pediatric dermatology March 23-24 for pediatricians and general practitioners. The guest lecturer will be Dr. Hamilton Montgomery, professor of dermatology at the University of Minnesota Graduate School, Rochester.

Margaret Beattie Lecture.—The second annual Margaret Beattie Lecture will be presented Feb. 4 at a dinner meeting at the St. Francis Hotel, San Francisco. Linus C. Pauling, Ph.D., chairman, division of chemistry and chemical engineering, California Institute of Technology, Pasadena, will discuss "Abnormal Hemoglobin Molecules in Relation to Hereditary Hemolytic Anemia." Dr. Pauling was awarded the Nobel prize in chemistry in 1954 and was the first recipient of the Thomas Addis medal of the National Nephrosis Foundation in 1955. The meeting is sponsored by the California Association of Clinical Laboratories and the western section of the Council of American Bioanalysts. A cordial invitation is extended to anyone interested. Price of the dinner is $5.75. Reservations may be obtained from Dr. Robert H. Pfeifer, Pacific Medical Laboratory, 760 Market St., San Francisco.

CONNECTICUT

Society News.—The Yale chapter of Alpha Kappa Kappa medical fraternity was addressed on Jan. 19 by Dr. Paul Dudley White, Boston, who discussed "The Ways of Life and Heart Disease."——The Connecticut State Medical Society has broken ground for an addition to its headquarters building in New Haven that will provide a small auditorium, a new conference room, and additional office space for the public relations section. The original building was built by the society and first occupied in 1949. The Connecticut Medical Examining Board, the special advisory committee to Selective Service, and the Connecticut Hospital Association also have offices in the building.

Dr. Nurnberger Goes to Indiana.—Dr. John I. Nurnberger, director of clinical laboratories at the Institute of Living, Hartford, has accepted the chairmanship of the department of psychiatry at the Indiana University School of Medicine, Bloomington-Indianapolis. Dr. Nurnberger, who is interested in stress-induced cell chemical changes in the nervous system, is co-editor of an annual symposium volume on brain metabolism. He was a research fellow at the Medical Nobel Institute for Cell Research and Genetics at Stockholm, Sweden, before assuming his present position with the Institute of Living and with Yale University School of Medicine, New Haven, where he has been assistant clinical professor of medicine (neurology) and psychiatry.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

DISTRICT OF COLUMBIA

Society News.—The American Hearing Society, which has been located at 817 14th St., N. W., in Washington, D. C., since 1948, has moved to 1800 H St., N. W., Washington 6, D. C., where its headquarters occupy the 12th floor.

Pictorial Exhibit of Presidential Physicians.—Physicians to the President of the United States are honored in a special pictorial exhibit (Jan. 1-March 31) in the gallery of medical history of the Smithsonian Institution (Smithsonian Arts and Industries Building, 9th and Jefferson Drive, Washington, D. C.). The exhibit, sponsored by the arts section of the Armed Forces Medical Library, includes portraits of physicians to Presidents Washington, Jefferson, Jackson, Lincoln, Cleveland, Taft, Harding, Hoover, Franklin D. Roosevelt, and Eisenhower.

Personal.—Dr. Thomas M. Peery, professor of pathology, George Washington University School of Medicine, Washington, D. C., was invited by the University of Puerto Rico, San Juan, to serve as visiting professor in pathology the first week of November.——Dr. Reaumur S. Donnally, Washington, D. C., has been named advisory editor on medicine for the Encyclopedia Americana.——Dr. Paul F. Dickens, professor emeritus of clinical medicine, George Washington University School of Medicine, Washington, D. C., has received the University of Tennessee's Certificate of Merit in recognition of his 50 years of service "to members of his community, both in the U. S. Navy and in civil life." Dr. Dickens has served as a member of the faculty of George Washington University, assistant professor of medicine at Georgetown University School of Medicine, Washington, D. C., and as professor of medicine at the U. S. Naval Medical School, Bethesda, Md., where he retired from active duty as a lieutenant commander in 1938.

ILLINOIS

Psychiatric Lecture.—Dr. Otto Billig, associate professor of psychiatry, Vanderbilt University School of Medicine, Nashville, Tenn., will present "The Management of Emotional Reactions in the Male Involutional Period" Feb. 1, 8 p. m., at the North Shore Health Resort, 225 Sheridan Rd., Winnetka. All physicians are invited.

Identification Wanted by F. B. I.—The Federal Bureau of Investigation is trying to identify a man who has a conspicuous 3-in. X-shaped scar on his right or left cheek and jaw; descriptions obtained from witnesses indicate it may be on either. Indications are that this man is from Illinois and that this scar resulted from a recent accident. On Dec. 7, 1955, the scar looked as though it was still healing, and stitch marks were still visible. At that time the area around his eyes was discolored. This man is a Caucasian, 22 to 26 years of age, between 5 ft. 5 in. and 5 ft. 8 in. tall, and weighs 135 to 140 lb. He is slender and has short, thick, blond hair, possibly cut flat top. Any physician who has treated a man resembling this person for an injury of the type described in recent months should communicate by collect telephone with the Federal Bureau of Investigation at either Chicago, telephone RAndolph 6-2150, or Springfield, telephone 2-9675. No effort should be made to hold or detain this man. Information furnished the F. B. I. will be held in strict confidence.

Chicago

Dr. Keeton Awarded Medal.—Dr. Robert W. Keeton will be the first recipient in the medical profession of the F. Paul Anderson medal of the American Society of Heating and Air-Conditioning Engineers, when it is presented at the 62nd annual meeting of the society, Jan. 23-25 in Cincinnati. Dr. Keeton retired from the staff of the University of Illinois College of Medicine in 1951 after 26 years as professor and head of the department of internal medicine. He has been active since 1935 in the society's cooperative research at the University of Illinois College of Medicine on man's physiological adjustment to environment.

Herrick Memorial Lecture.—The first James B. Herrick Memorial Lecture, "Clinical Management of Congestive Heart Failure Including Certain Aspects of Its Relationship to Venous Tone," will be presented at the Palmer House, Jan. 24, by Dr. George E. Burch, chairman, department of medicine, Tulane University of Louisiana School of Medicine, New Orleans, under the sponsorship of the Chicago Heart Association. A dinner at 6:30 p. m. ($5.25 per plate, including tax and gratuity) will precede the lecture (8 p. m.). The dinner and lecture are open to all physicians. Reservations should be made through the Chicago Heart Association, 69 W. Washington St., Chicago 2 (telephone: FInancial 6-4675). Telephone for physicians' calls during the meeting: RA 6-7500.

Lecture on Radioactive Isotopes.—In its Monday lectures on the uses of radium, radioisotopes, and x-rays in diagnosing and treating diseases (7-9 p. m. at St. Luke's Hospital), Northwestern University Medical School will present "Technic in the Uses of Radioactive Isotopes in the Diagnosis and Treatment of Diseases" by John A. D. Cooper, Ph.D., associate professor of biochemistry, Feb. 2. Dr. Edward L. Jenkinson, professor of radiology at the medical school, is in charge of the lectures, given in honor of Dr. James T. Case, Santa Barbara, Calif., professor emeritus of radiology at Northwestern. The lectures are given by staff members from Northwestern University Medical School, the Mayo Clinic in Rochester, Minn., and the University of Illinois College of Medicine.

MASSACHUSETTS

Tufts Medical Alumni Lecture.—The annual medical alumni lecture at Tufts College Medical School, Boston, will be given Jan. 31, 4 p. m., by Dr. Christopher J. Duncan, associate chief surgeon at Free Hospital for Women, Brookline, and clinical associate in gynecology at Harvard Medical School. His subject will be "The Care of the Female Patient." All students and physicians are invited.

Research in Atherosclerosis.—The John A. Hartford Foundation has established a memorial fund in the school of public health of Harvard University, Boston, to support a research program. The foundation agrees to provide $200,000 annually for several years, to "institute, maintain and carry out a program of basic scientific and medical research to determine the causes and the medical or other treatment which will prevent or cure or alleviate human suffering from atherosclerosis and related diseases of the human heart and blood vessels" and for graduate education in this field. The program of research and graduate education will be carried out primarily in the department of nutrition, of which Dr. Fredrick J. Stare is the head. It will include an intensive laboratory study on experimental animals; clinical observations in cooperation with medical staffs of hospitals in Boston and elsewhere; and integration of these with field studies.

MICHIGAN

Society News.—The Blackwell Society will hold a dinner meeting Jan. 25, 6:30 p. m., at David Whitney House, Detroit. A symposium, "Rheumatic Heart Disease," will be presented with Dr. Margaret A. Baima as moderator and Drs. Ruth M. Kraft, Detroit, William B. McIntyre, Detroit; Joan C. Stryker, Wyandotte; and James B. Blodgett, Detroit, as collaborators.

Annual Symposium on Blood.—The Wayne University College of Medicine offers the fifth annual Symposium on Blood Jan. 21 in the auditorium, 645 Mullett St. Presentations by out-of-state speakers include:

Biochemical Studies on Leukocytes, William N. Valentine and John S. Lawrence, Los Angeles.
Aplastic Anemia: Natural History and Incidence in Modern Therapy, James A. Wolff, Hattie E. Alexander, Allyn B. Lie, and Frances Rowe, New York.
Slow and Rapid Freezing of Blood: Mechanisms of Cell Injury and Its Prevention, Harold T. Meryman, Bethesda, Md., and New Haven, Conn.
Role of Plasma Thromboplastin Component (PTC) in Blood Coagulation, Theodore H. Spaet, San Francisco.
Action of Platelets and Tissue Fractions on Hemostasis, Edmund Klein and Sidney Farber, Boston.
New Serum Factor (Factor X), F. Druckert, P. Fluckinger, and F. Koller, Zurich, Switzerland.
Anaphylaxis, Radiation and Heparin, Frank C. Monkhouse, Toronto, Canada.
Some Effects of Proteolytic Enzyme Inhibitors on Blood Coagulation, N. Raphael Shulman, Bethesda, Md.
Studies on Activation of the Fibrinolytic Enzyme in Human Plasma by Streptokinase, Sol Sherry, St. Louis.
Studies on Thrombin Formation, Hans F. Jensen, Fort Knox, Ky.

Annual Public Relations Seminar in Detroit.—The Michigan State Medical Society will present the annual County Secretaries-Public Relations Seminar, Jan. 27-29, at the Sheraton-Cadillac Hotel, Detroit, under the cochairmanship of Drs. Howard G. Benjamin and C. Allen Payne, Grand Rapids. The theme of the seminar is "You Are Organized Medicine's Basic Unit." On Friday a get-acquainted reception (5:30 p. m.) and dinner (6:15 p. m.) will precede the general assembly (8 p. m.) at which Dr. William S. Jones, Menominee, the society's president, will moderate the following panel, "Four Basic Threats to Health Welfare":

Mac F. Cahal, J.D., Kansas City, Mo., executive director, American Academy of General Practice, Encroachment of Ancillary Groups.
Robert L. Novy, Detroit, past-president, Michigan Medical Service (1942-1955), Medical Practice by Business.
Mr. Albert E. Blashfield, Ann Arbor, president, State Bar of Michigan, Corporate Practice of Medicine.
A. E. Johansen, Battle Creek, congressman, third district of Michigan, Broader Socialization Schemes.

The Saturday morning program will include the following presentations:

Will Government Rule Medicine Through Compulsory Disability Insurance? R. G. Van Buskirk, LL.B., Chicago.
Medicolegal Problems, J. Joseph Herbert, J.D., Manistique.
Medical Service and Public Relations, Mr. Hugh W. Brenneman, Lansing, director of public relations, Michigan State Medical Society.
Social and Economic Aspects of Medicine, Ernest B. Howard, Chicago, Assistant Secretary, American Medical Association.

Saturday afternoon will open with "Experts at Bay," a program involving discussions on hospital relations, veterans' problems, Blue Shield, medical organization (including membership), 24-hour medical service, legislative matters, indoctrination, public relations and communications, medicolegal problems, county society planning, doctor placement, licensure, fees, medical management, and community service. At 3:40 p. m. Dr. Clarence D. Selby, Port Huron, will preside at a session, "Medical Organization: Its Strength and Weakness," in which "The New MSMS Organization Handbook" will be considered by Dr. L. Fernald Foster, Bay City, and William J. Burns, LL.B., Lansing. The conference will conclude Sunday, 1:15 p. m., with an address, "The Job Is Yours," by Dr. Julian P. Price, Florence, S. C., a Trustee of the American Medical Association.

NEBRASKA

Warning Against Impostors.—The Nebraska State Medical Association has issued a warning, especially to rural communities having no physician, concerning persons without a license to practice medicine or the qualifications to receive one who have attempted to set up practices in small communities. The association points out that these persons may have had some contact with medicine, possibly through the armed forces or in some hospital. It advises that all communities having a new practitioner coming in to set up a practice should check his credentials carefully and, if there is any doubt as to his qualifications, apply to the Nebraska State Medical Association, 1315 Sharp Building, Lincoln, or the State Department of Health, State Capitol, Lincoln, for a thorough check.

NEW JERSEY

Hospital News.—The Atlantic City Hospital will have as visiting chiefs pro tem. Dr. Milton Rapoport, professor of pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Jan. 23-27, and Dr. Harry Gold, professor of clinical pharmacology, Cornell University Medical College, New York, Jan. 30-Feb. 3.

Cardiology Fellowships Available.—St. Michael's Hospital, Newark, will have available beginning July 1 two clinical trainee fellowships in cardiology, recognized by the National Heart Institute and credited toward one year of residency in internal medicine. To qualify, an applicant must have completed two years of an approved residency in internal medicine. Those interested should communicate promptly with Dr. Nicholas A. Antonius, Director, Department of Cardiology, St. Michael's Hospital, Newark.

NEW YORK

Doctors' Symphony Orchestra.—The Brooklyn Doctors' Symphony Orchestra gave a concert Dec. 16, 1955, for the benefit of the library fund of the Kings County Medical Society, with Miss Barbara Lieberman, violinist, as guest soloist. Rehearsals of the orchestra are held every Wednesday at 8:30 p. m. in the auditorium of the Brooklyn High School for Home-Making, 901 Classen Ave. For details call Dr. Benjamin A. Rosenberg, Brooklyn, at NEvins 8-2370.

Personal.—Dr. Bruno W. Volk, director of laboratories, Jewish Chronic Disease Hospital, Brooklyn, has also been appointed director of the recently organized Isaac Albert Research Institute of the hospital.——Dr. Herman E. Hilleboe, Albany, state health commissioner, has been named by Gov. Harriman as one of three members of a council on the use of nuclear materials that will establish a coordinated state program on the peaceful uses of atomic energy.——J. Garth Johnson, Ph.D., professor of public health, Albany Medical College of Union University, has been appointed general chairman of the Albany Regional Health Conference, which will be held in early April at a site to be selected in the Albany area.——Dr. Allison J. Vosseler has been appointed director of surgery of the Methodist Hospital, Brooklyn, where he has been attending surgeon since 1938. For many years Dr. Vosseler was associated with his father, the late Dr. Theodore L. Vosseler, who was also on the staff of Methodist Hospital. Dr. Allison Vosseler is on the staff at Carson C. Peck Memorial Hospital and has served as director of surgery at the John E. Jennings Hospital of Kings County Hospital Center. He is a past-president of the Brooklyn Surgical Society and president of the Brooklyn chapter, Pan American Medical Association. He is the founder and sponsor of the Theodore L. Vosseler Memorial Scholarship at the Columbia University College of Physicians and Surgeons.

New York City

Society News.—At the meeting of the Bronx Society of Neurology and Psychiatry at the Veterans Administration Hospital, 3A Conference Room, 130 W. Kingsbridge Rd., Bronx, Jan. 26, 8:30 p. m., Dr. Paul V. Lemkau, director of mental health services, will outline "The Work and Opportunity of the New York City Community Mental Health Board."

Course in Cancer Detection.—A course in exfoliative cytology will be given from March 5 to June 1 at Cornell University Medical College, 1300 York Ave., New York 21. The course, open to a limited number of physicians and technicians affiliated with hospital laboratories, will cover the cytology of the female genital, gastrointestinal, respiratory, and urinary tracts, as well as exudates. Arrangements for shorter periods of instruction covering certain applications of exfoliative cytology may be made for those who are unable to take the entire course. Tuition for the course is $300 (proportionate for shorter periods). Instruction is under the direction of Drs. George N. Papanicolaou and John F. Seybolt. Requests for information should be addressed to Dr. Seybolt.

OHIO

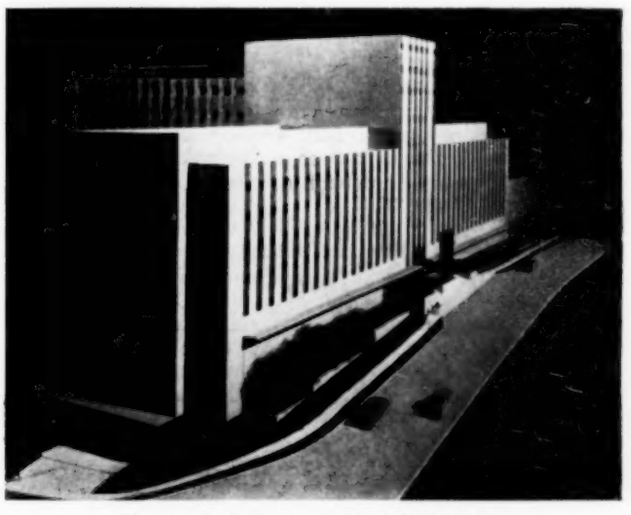
Course on General Practice.—The Frank E. Bunts Educational Institute, affiliated with the Cleveland Clinic Foundation, announces a course, Feb. 8-9, approved for 10 hours' credit and sponsored by the Cleveland chapter of the American Academy of General Practice. The course, which is open to all members of the medical profession, will be presented at the institute, 2020 E. 93rd St., Cleveland 6. The guest speaker, Dr. Frederick C. Robbins, professor of pediatrics, Western Reserve University School of Medicine, Cleveland, will discuss "The Present Status of Poliomyelitis Vaccine" at 10 a. m. Wednesday. The afternoon session will end with a panel discussion on acute surgical emergencies, moderated by Dr. George Crile Jr., Cleveland. The course will terminate Thursday, 12:50 p. m., with a panel discussion, "Acute Medical Emergencies" for which Dr. Arthur C. Ernstene, Cleveland, will serve as moderator.

OKLAHOMA

Pediatrics Lecture.—Dr. Daniel V. Jones, associate professor of pediatrics, University of Cincinnati College of Medicine, will be guest speaker for the Tulsa Academy of General Practice at a dinner meeting at the Hotel Tulsa open to all physicians Jan. 23, 8 p. m. His subject will be "The Problem of the Premature and Newborn Infant." Reservations may be made by calling LUther 2-5904.

PENNSYLVANIA

Schools of the Health Professions.—The University of Pittsburgh is constructing a 15-million-dollar building, featuring movable walls to permit use of space in units of varying sizes, adjustable to the changing needs of the various departments, and entrances



Model of Schools of the Health Professions.

on three levels, for the Schools of the Health Professions, including medicine, pharmacy, dentistry, and nursing. The T-shaped building is 13 stories high with 10-story wings and a 5-story auditorium. It will connect directly to Presbyterian, Woman's, and Eye and Ear hospitals, three of eight hospitals affiliated with the university's medical program. In the 550,000 square feet of the structure's floor space will be facilities for teaching, departmental offices, and research activities as well as a student center, library, lecture rooms, and an auditorium.

Philadelphia

Rehabilitation Course.—The favorable response to the initial presentations by the University of Pennsylvania of the course, "Principles of Rehabilitation," has resulted in future scheduling for the following dates: Feb. 6-11; April 2-7; and June 25-29. The course is open to physicians, registered nurses, occupational therapists, social workers, rehabilitation counselors, and others concerned with rehabilitation of the handicapped. Provisions for granting a limited number of trainee stipends to eligible persons attending the course have been made by the U. S. Office

of Vocational Rehabilitation. Applications for these stipends and details concerning the course may be addressed to the Rehabilitation Center, Hospital of the University of Pennsylvania, Philadelphia 4.

Personal.—Dr. David Myers, who has served as associate of otorhinology at Temple University School of Medicine for 15 years, has been named professor and head of the department of otorhinology.——Dr. Russell S. Boles delivered the Julius Friedenwald Memorial Lecture, "An Appraisal of the Medical Versus Surgical Treatment of Gastrointestinal Disorders," at the University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, Nov. 3, 1955.——Dr. Alma Dea Morani was presented with the first woman's award of the Order of the Sons of Italy in America at a meeting in the Bellevue Stratford, Oct. 14, 1955.——Dr. Robert A. Clark, formerly director of the Mental Health Clinic at Western Psychiatric Institute and Clinic in Pittsburgh and associate professor of psychiatry at the University of Pittsburgh School of Medicine, has assumed his duties as clinical director at Friends Hospital, where he will also serve as chief of the outpatient department and director of the training program for resident physicians.——Dr. L. Earle Arnow, director of research of Sharp & Dohme, was awarded the University of Minnesota Outstanding Achievement award at the 128th national meeting of the American Chemical Society at the University of Minnesota, Minneapolis. Dr. Arnow is a graduate of the University of Minnesota and for many years was a member of its medical faculty.

TEXAS

Course on Cardiology.—Dr. Samuel A. Levine, clinical professor of medicine, Harvard Medical School, Boston, will present a course in practical bedside cardiology, March 14-17, at the Texas Medical Center, Houston. Dr. Levine will be the first lecturer for the James J. and Una Truitt endowed chair in cardiology at the University of Texas Postgraduate School of Medicine. The course (registration fee $35) will be cosponsored by the Baylor University College of Medicine and the Houston Heart Association. Application should be made to the University of Texas Postgraduate School of Medicine, Texas Medical Center, Houston 25.

Occupational Health Director Wanted.—The Texas State Department of Health announces examinations for an occupational health director (salary range: $9,720-$12,120), who shall be responsible for developing and directing a state-wide program of occupational health designed to control and prevent occupational diseases and hazards. Applicants must be citizens of the United States. The minimum qualifications are (1) M.D. degree and 1 year's internship in a recognized hospital; (2) M.P.H. degree, or certification by the American Board of Preventive Medicine, or six years of experience in industrial medicine or the private practice of medicine in an industrial setting, three years of which should be in a public health agency; and (3) licensure to practice medicine in Texas. For applications write: Merit System Council, 814 Littlefield Bldg., Austin, or Dr. Henry A. Holle, Commissioner of Health, Texas State Department of Health, 410 E. Fifth St., Austin.

UTAH

Course on Anesthesiology.—The University of Utah College of Medicine, Salt Lake City, will offer a course in anesthesiology for part-time anesthesiologists in the University of Utah affiliated hospitals, Feb. 13-18. The speaker will be Dr. James E. Eckenhoff, professor of anesthesiology, University of Pennsylvania School of Medicine, Philadelphia. The course will include consideration of "Respiration and Techniques," "Regional Anesthesia," "Cardiovascular Effects of Anesthesia," "Intravenous Agents," and "Endotracheal Anesthesia." Hospital observation and practice will be available at 7 a. m. daily in assigned Salt Lake City hospitals. Round-table luncheon discussions will be held Monday (premedication), Tuesday (choice of anesthetic), Friday (relaxants), and Saturday (deaths associated with anesthesia) at Evan's Cafe; and Wednesday (special anesthesia) and Thursday (shock during anesthesia) at Brattens. The Salt Lake County Medical Society will meet at Moreau Hall at 7:30 p. m. Monday. Tuesday evening the anesthesiology residents' weekly case conference and the Journal Club will meet in the conference room of the Salt Lake General Hospital at 7:15 p. m., and the Audubon Screen Tour series will be presented in Kingsbury Hall at 8 p. m. The Utah Symphony will give a Mozart Cycle in Kingsbury Hall Wednesday evening. The Utah State Society of Anesthesiologists plan a special dinner at the University Club Thursday evening. The University of Utah weekly anesthesia conference will consider "Anesthetic Problems During Pulmonary Surgery" Friday evening, and the weekly surgical conference will be held Saturday morning. A basketball game (Utah vs. Denver) is scheduled for 7:30 p. m. Saturday.

WASHINGTON

Surgeons Meet in Seattle.—The annual meeting of the Seattle Surgical Society will be held at the Olympic Hotel Jan. 27-28. The guest speaker, Dr. Charles B. Puestow, clinical professor of surgery, University of Illinois College of Medicine, Chicago, will discuss the papers presented by members of the society and will deliver an address. All physicians are invited. Tickets for the Friday evening banquet and Saturday luncheon may be obtained at the time of the meeting.

WISCONSIN

Society News.—The Wisconsin Radiological Society recently named Dr. Ralph C. Frank, Eau Claire, president; Dr. Lester W. Paul, Madison, president-elect; and Dr. William W. Moir, Sheboygan, secretary-treasurer.

Conference on Interprofessional Cooperation.—In celebration of its 75th anniversary, Marquette University, Milwaukee, will present "Interprofessional Cooperation for the Improvement of Our Health and Welfare," the third of five major academic conferences, Jan. 23-26 at Brooks Memorial Union. Dr. John S. Hirschboeck, dean of Marquette University School of Medicine, chairman of the conference, announces the following panelists: Dr. Robert A. Moore, vice-chancellor of the Schools of the Health Professions, University of Pittsburgh; Dr. Robin C. Buerki, executive director of the Henry Ford Hospital, Detroit; Dr. Stanley E. Dorst, dean of the University of Cincinnati College of Medicine; Maynard K. Hine, D.D.S., dean of Indiana University School of Dentistry, Indianapolis; Dr. Howard A. Rusk, chairman of the department of physical medicine and rehabilitation of New York University-Bellevue Medical Center, New York City; and Dr. Herman G. Weiskotten, dean emeritus of Syracuse (N. Y.) University College of Medicine. The talks will be open to the public. The views expressed by the panelists will be examined in closed seminars attended by an invited group of specialists in the medical and related fields involved. The questions to be considered include: How should the boundaries between specialists be established? Who should be responsible for hospital operation, medical education, and the dispensing of drugs? Is the importance of some diseases being overemphasized? Who should raise and control funds for medical research?

GENERAL

For Physician Philatelists.—Recent issues of postage stamps of interest to physician philatelists include:

Netherlands: Five special stamps (microscope and crab), each stamp with a surcharge to help in the fight against cancer.

Australia: A 3½ d. stamp in honor of the nursing profession, with Florence Nightingale as a background figure.

Italy: In observation of International Medical Day, a 25-lire stamp portraying Girolamo Fracastoro (1483-1553), physician, mathematician, philosopher, and personal physician to Pope Paul III.

Yugoslavia: A nine-value series showing the medicinal plants and flowers of that country, printed in natural color.

Israel: A 160-pruta stamp, to commemorate the 25th anniversary of Magen David Adom, the Israeli equivalent of the Red Cross.

Finland: A series of three stamps with a surcharge for the benefit of the Red Cross.

Meeting on Surgery of the Hand.—The American Society for Surgery of the Hand will hold its 11th annual meeting at the Palmer House, Chicago, Jan. 27, under the presidency of Dr.

S. Benjamin Fowler, Nashville, Tenn. The following invitational addresses have been scheduled:

Rupture of Extensor Tendons in the Rheumatoid Hand, L. Ramsay Straub and Edward H. Wilson, New York City.
Anatomy of the Hand, Ernest W. Lampe, New York City.
Carpal Tunnel Syndrome, Bland W. Cannon, Memphis, Tenn.
Congenital Deformities of the Hand, Herbert Conway and John Bouve, New York City.

The session will close with "The Surgical, Social and Economic Aspects of a Unit Hand Injury" by Dr. William Metcalf and Dr. William P. Whalen, New York (by invitation). The members' dinner will be held Friday, 7 p. m., and a clinical program for members only and invited guests will be presented Saturday morning.

Psychiatric Research Symposium.—In cooperation with the American Psychiatric Association, the department of psychiatry of the University of California School of Medicine at Los Angeles and the University of California University Extension will hold a western regional research symposium, "Application of Basic Science Techniques to Psychiatric Research," in room 2147 of the University of California at Los Angeles Life Sciences Building, Jan. 26-27. The course is open to psychiatrists, psychologists, psychiatric social workers, psychiatric nurses, and others with the consent of the course chairman, according to Dr. Thomas H. Sternberg, assistant dean for postgraduate medical education at the University of California at Los Angeles. Topics will include Brain Mechanisms and Behavior, Experimental Studies of Psychosomatic Disease, Methods of Blocking Neuroendocrine Mechanisms, and Brain Metabolism. Requests for information and registration blanks should be addressed to Dr. Thomas H. Sternberg, University of California School of Medicine, Los Angeles 24. Fee for the symposium, $3.50, is payable to the Regents of the University of California. A cocktail party at the Beverly Hills Hotel for all who attend, including wives, is set for 7 p. m., Thursday.

Surgical Fellowships in Orthopedics.—The National Foundation for Infantile Paralysis has instituted a fellowship program for surgeons interested in advanced study to prepare themselves for teaching or research in orthopedics. Applicants must have completed requirements for certification by the American Board of Orthopedic Surgery or have had equivalent training. Only United States citizens, licensed to practice medicine, in sound health, and under 36 years of age, will be eligible. Each candidate must arrange his own program for full-time study and investigation at a center that has been approved by the Council on Medical Education and Hospitals of the American Medical Association for residency training in orthopedic surgery and that is associated with an approved medical school. Appointments will be made for one year, but renewal of the fellowship may be requested. Financial benefits will be determined on the basis of individual need as related to marital status and number of dependents. Selection of candidates to be appointed as fellows will be made on a competitive basis by the National Foundation's clinical fellowship committee. For consideration in May, applications must be filed by March 1; for review in November, applications must be received by Sept. 1; and for action in February, by Dec. 1. For further information and application forms, address: Division of Professional Education, National Foundation for Infantile Paralysis, 120 Broadway, New York 5.

Western Meetings on Clinical Research.—The annual meeting of the Northwest Society for Clinical Research will convene in the auditorium of the University of Oregon Medical School, Portland, Jan. 21, under the presidency of Dr. George B. Long, Portland. The scientific program will open at 9:15 a. m. with presentation of "Recent Advances in Porphyrin Metabolism" by Dr. Robert A. Aldrich, Portland, and will end at 4 p. m. with "Primary Chylopericardium" by Dr. Marvin Schwartz, Portland. In all, 16 papers will be read. A no-host luncheon is scheduled at the University Club. Cocktails, 7-8 p. m., will precede the dinner dance.——The annual meeting of the western section of the American Federation for Clinical Research will convene at the Golden Bough Theatre, Carmel, Calif., at 9 a. m., Jan. 26. Fifty speakers will participate by invitation in presentation of the 24 papers that have been scheduled. Dr. Belding H. Scribner, Seattle, will preside.——The Western Society for Clinical Research will hold its ninth annual meeting at the Golden Bough Theatre, Jan. 27-28 at Carmel, Calif. The president's address by Dr. Travis Winsor, Los Angeles, will open the session Friday at 9 a. m. The Friday afternoon meeting will open with an address, "Deranged Cholesterol Metabolism," by Dr. Meyer Friedman, San Francisco, and the Saturday morning program with "Erythron Dynamics" by Dr. Joseph Ross, Los Angeles. In addition, 49 papers will be presented. A specialty session is scheduled for Saturday morning.

Orthopaedic Surgeons Meet in Chicago.—The American Academy of Orthopaedic Surgeons will hold its 23rd annual meeting Jan. 28-Feb. 2 at the Palmer House, Chicago. The presidential address will be delivered Monday at 11:30 a. m. by Dr. Walter P. Blount, Milwaukee. The scientific program will be preceded by instructional courses, which will also run concurrently. In all, 96 instructional courses will be presented. At 11 a. m. Monday the scientific session will open with "The Use of Cutis as an Interposing Membrane in Arthroplasty of the Knee" by Drs. Joseph E. Brown, Wilbert H. McGaw, and Darrel T. Shaw (by invitation), all of Cleveland. At 4 p. m. Mr. John O. Moore, director of automotive crash injury research, department of public health and preventive medicine, Cornell University Medical College, New York, will give an invitational address, "Automotive Crash Injury Research." A film produced by Mr. Moore, "Automotive Crash Safety Research at Cornell University," will be shown at 4:30 p. m. and will be followed by a film, "Poliomyelitis: Flexion and Extension Tenodesis in the Hand," produced by Dr. Charles E. Irwin, Atlanta, Ga. "Surgical Treatment of Spinal Tuberculosis" will be discussed by Dr. Philipp J. Erlacher, Vienna, Austria, (by invitation) Tuesday at 11:30 a. m. "The Walter Reed Report on Cineplasty: A Critical End Result Study" will be given at 2:30 p. m., Tuesday, by Col. Ernest A. Brav, M.C., Washington, D. C.; Col. August W. Spittler, M.C.; and Lieut. Col. Maurice J. Fletcher, M.S.C., Washington, D. C. (by invitation). The International Society for Orthopaedic Surgery and Traumatology will hold a dinner meeting Tuesday at 7 p. m. The annual banquet is scheduled for Wednesday evening. About 250 participants are listed for the instructional and scientific sessions.

Society News.—Newly elected officers of the **American Society of Tropical Medicine and Hygiene** include: Justin M. Andrews, Sc.D., Washington, D. C., president-elect, and Willard H. Wright, Ph.D., Bethesda, Md., vice-president.——Newly elected officers of the **American Rheumatism Association** include: Dr. Charles L. Short, Boston, president; Dr. William D. Robinson, Ann Arbor, Mich., first vice-president and president-elect; Dr. William H. Kammerer, New York, second vice-president; and Dr. Edward F. Hartung, New York, secretary-treasurer.——Newly elected officers of the **Radiological Society of North America** include: Dr. Clarence E. Hufford, Toledo, Ohio, president; Dr. E. Edgar Virden, Kansas City, Mo., president-elect; Drs. James E. Lofstrom, Detroit, Peter E. Russo, Oklahoma City, and Walter H. Ude, Minneapolis, vice-presidents; and Dr. Donald S. Childs, Syracuse, N. Y., secretary-treasurer.——Newly elected officers of the **American Academy for Cerebral Palsy** include: Dr. Margaret H. Jones, Pacific Palisades, Calif., president; Dr. Nicholson J. Eastman, Baltimore, president-elect; and Dr. Robert A. Knight, Memphis, Tenn., secretary-treasurer. The 1956 meeting will be held in Chicago in the fall, and the 1957 meeting in New Orleans.——Officers of the **American Academy of Obstetrics and Gynecology** include: Dr. Ralph E. Campbell, Madison, Wis., president; Dr. R. Gordon Douglas, New York, president-elect; Dr. Norman F. Miller, Ann Arbor, Mich., first vice-president; Dr. Duncan E. Reid, Boston, second vice-president; Dr. C. Paul Hodgkinson, Detroit, secretary; Dr. Herbert E. Schmitz, Chicago, treasurer; and Dr. John C. Ullery, Columbus, Ohio, assistant secretary.——The southern section of the **American Laryngological, Rhinological and Otological Society** will meet in the Shamrock Hotel, Houston, Texas, Jan. 27-28. A postconvention trip by chartered bus to Monterrey, Mexico, is scheduled, leaving the hotel at 6 a. m., Jan. 29, and returning to Houston Wednesday evening. Complete information may be had from Dr. Jehu M. Robison, Vice-President, Southern Section, 1304 Walker Ave., Houston 2, Texas.

Meeting of Obstetricians and Gynecologists.—The South Atlantic Association of Obstetricians and Gynecologists will hold its 18th annual meeting at the Hollywood Beach Hotel, Hollywood, Fla., Jan. 29-Feb. 1 under the presidency of Dr. Waverly R. Payne, Newport News, Va. The following case reports will be made by invitation Monday morning:

Dysgerminoma Complicating Labor, Stephen L. Watson, Lakeland, Fla.
Twin Pregnancy with One Twin Blighted, Richard C. Forman, Coral Gables, Fla.
Double Vagina and Uterus Unicornis—Repair of Vagina and Subsequent Term Delivery, A. Erskine Sproul, Staunton, Va.
Carcinoma of the Cervical Stump, Unusual Case, Joseph W. Scott, Miami, Fla.
Spontaneous Rupture of a Uterine Varix in Pregnancy at Twenty-Eight Plus Weeks, T. Vernon Finch, Sarasota, Fla.

The case reports will be discussed by a panel consisting of Dr. R. Gordon Douglas, New York City, moderator, and Drs. John L. Parks, Washington, D. C., Frank R. Smith, New York City, and Franklin L. Payne, Philadelphia. "Mastopathy as Related to Functional Uterine Disease" by Dr. William E. Byrd (by invitation), Norfolk, Va., will precede "Essentials of Endometrial Pathology" by the guest speaker, Dr. Arthur T. Hertig, Boston. Tuesday morning "Afibrinogenemia" by Drs. Christopher J. Murphy Jr. (by invitation), P. Harrison Picot, and H. Glenn Thompson, Alexandria, Va., and "Tubal Ligation—Its Use and Abuse" by Dr. Willard C. Hearin Jr. (by invitation), Greenville, S. C., will precede "The Teaching of Gynecologic Cancer Therapy to the Physician" by Dr. John C. Ullery, Columbus, Ohio, guest speaker. The presidential address at 12 noon will follow "The Role of Retained Placental Fragments in Immediate and Delayed Postpartum Hemorrhage" by Drs. William M. Lester (by invitation), Rudolph A. Bartholomew, Emmett D. Colvin, William H. Grimes Jr., John S. Fish, and William H. Galloway, Atlanta, Ga. The president's party, 6:30 p. m., will precede the banquet, 7:30 p. m. The Wednesday program will open with "The Routine Colpotomy" by Dr. Jesse B. Caldwell (by invitation), Gastonia, N. C., and "The Function of a Tissue Committee in Obstetrics and Gynecology" by Dr. Vernon B. Moore (by invitation), Greenwood, S. C.

CANADA

Meeting on Rehabilitation.—The Canadian Association of Physical Medicine and Rehabilitation will hold the fourth annual meeting June 1-2, in London, Ontario. All inquiries or information regarding the presentation of papers should be addressed to the secretary, Dr. Gustave Gingras, 6265 Hudson Rd., Montreal.

LATIN AMERICA

Gerontological Congress.—The first Pan American Congress on Gerontology, which will convene in Mexico City, Mexico, Sept. 7-15, invites those who wish to present papers at the congress to send abstracts of not more than 200 words to Dr. Edmund V. Cowdry, Washington University School of Medicine, St. Louis 10, before April 1, mentioning whether lantern slides will be shown. Dr. Cowdry is chairman of the North American committee of cooperation.

FOREIGN

Seminar Congresses in Internal Medicine.—In its seminar congresses in internal medicine, the American Medical Society of Vienna, Vienna, Austria, will present the following programs by the medical faculty of the University of Vienna:

March 1-3, Hematology; Heart Diseases; Electrocardiology.
April 5-7, Allergy—Arthritis.
May 3-5, Heart Diseases; Cardiovascular Diseases; Peripheral Vascular Diseases.
June 4-6, Cardiology; Electrocardiology; Vectorcardiography—Ballistocardiograph.
July 5-7, Diabetes; Liver and Biliary Tract Diseases; Hypertension and Nephritis.
Aug. 2-4, Endocrinology; Metabolism; Fluid and Electrolyte Balance.
Sept. 3-5, Gastroscopy; Gastroenterology; Proctology.
Oct. 8-10, Hematology; Normal Peripheral Blood and Bone Marrow; Diseases of the Blood and Blood-Forming Organs.
Nov. 5-7, Diseases of the Chest; Tuberculosis; Malignant Diseases.

Details may be obtained from the American Medical Society of Vienna, Vienna I. Universitaetsstrasse 11. Cable: "Ammedic" Vienna.

CORRECTION

Reactions to Mycostatin by Vein.—In the Dec. 31, 1955, issue of THE JOURNAL, page 1803, the reply to an inquiry on Candida infections stated that Mycostatin, a new antibiotic preparation used against Candida infections, can be given intravenously. While originally this material was used intravenously, further investigation indicated that intravenous administration produced severe reactions. Large doses given orally are free of such side-effects and are as effective as was intravenous administration.

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. George F. Lull, 535 North Dearborn St., Chicago 10, Secretary.

1956 Annual Meeting, Chicago, June 11-15.

1956 Clinical Meeting, Seattle, Nov. 27-30.

1957 Annual Meeting, New York, June 3-7.

1957 Clinical Meeting, Philadelphia, Dec. 3-6.

1958 Annual Meeting, San Francisco, June 23-27.

ANNUAL CONGRESS ON INDUSTRIAL HEALTH, Sheraton-Cadillac Hotel, Detroit, Jan. 23-24. Mr. Clark D. Bridges, 535 N. Dearborn St., Chicago 10, Acting Secretary.

ANNUAL CONGRESS ON MEDICAL EDUCATION AND LICENSURE, Palmer House, Chicago, Feb. 11-14. Dr. Edward L. Turner, 535 N. Dearborn St., Chicago 10, Secretary.

NATIONAL CONFERENCE ON RURAL HEALTH, Multnomah Hotel, Portland, Ore., Mar. 8-10. Mrs. Arline Hibbard, 535 N. Dearborn St., Chicago 10, Secretary.

ALASKA TERRITORIAL MEDICAL ASSOCIATION, Alaska Native Health Service Hospital, Anchorage, Feb. 20-22. Dr. Robert B. Wilkins, 1121 Fourth Ave., Anchorage, Secretary.

AMERICAN ACADEMY OF ALLERGY, Chase Hotel, St. Louis, Feb. 6-8. Dr. Francis C. Lowell, 65 East Newton St., Boston, Secretary.

AMERICAN ACADEMY OF FORENSIC SCIENCES, Drake Hotel, Chicago, Feb. 23-25. Dr. Walter J. Camp, 1853 West Polk St., Chicago, Secretary.

AMERICAN ACADEMY OF OCCUPATIONAL MEDICINE, Netherlands-Plaza Hotel, Cincinnati, Feb. 15-17. Dr. Leonard J. Goldwater, 600 W. 168th St., New York 32, Secretary.

AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS, Palmer House, Chicago, Jan. 28-Feb. 2. Dr. John R. Norcross, 122 South Michigan Blvd., Chicago 3, Secretary.

AMERICAN COLLEGE OF RADIOLOGY, Drake Hotel, Chicago, Feb. 10-11. Mr. William C. Stronach, 20 North Wacker Drive, Chicago 6, Executive Secretary.

AMERICAN ORTHOPSYCHIATRIC ASSOCIATION, Hotel Commodore, New York, Mar. 15-17. Dr. Marion F. Langer, 1790 Broadway, New York 19, Executive Secretary.

AMERICAN SOCIETY FOR SURGERY OF THE HAND, Chicago, Jan. 27. Dr. George V. Webster, 1145 East Green St., Pasadena 1, Calif., Secretary.

CENTRAL SURGICAL ASSOCIATION, Hotel Kahler, Rochester, Minn., Feb. 23-25. Dr. Charles D. Branch, 102 North St., Peoria, Ill., Secretary.

CHICAGO MEDICAL SOCIETY ANNUAL CLINICAL CONFERENCE, Palmer House, Chicago, Feb. 28-March 2. Dr. Norris J. Heckel, 86 E. Randolph St., Chicago 1, Secretary.

DALLAS SOUTHERN CLINICAL SOCIETY, Dallas, Tex., Mar. 12-14. Miss Helga Boyd, 433 Medical Arts Bldg., Dallas 1, Tex., Executive Secretary.

EASTERN CONFERENCE OF RADIOLOGISTS, Lord Baltimore Hotel, Baltimore, Mar. 15-17. Dr. Richard B. Hanchett, 705 Medical Arts Bldg., Baltimore 1, Secretary.

MEDICAL SOCIETY EXECUTIVES CONFERENCE, Drake Hotel, Chicago, Feb. 6-8. Mr. H. Martin Baker, 1102 South Hillside, Wichita 17, Kansas, Secretary.

MICHIGAN CLINICAL INSTITUTE, Sheraton-Cadillac Hotel, Detroit, Mar. 7-9. Dr. L. Fernald Foster, 606 Townsend St., Lansing 15, Secretary.

NEW ORLEANS GRADUATE MEDICAL ASSEMBLY, Municipal Auditorium, New Orleans, Feb. 27-March 1. Dr. Eugene H. Countiss, Room 103, 1430 Tulane Ave., New Orleans 12, Director.

REGIONAL MEETINGS, AMERICAN COLLEGE OF PHYSICIANS:

PHILADELPHIA, Jan. 27. Dr. Thomas M. McMillan, 330 South 9th St., Philadelphia 7, Governor.

SASKATOON, SASK., Feb. 3-4. Dr. C. H. A. Walton, Winnipeg Clinic, Winnipeg, Man., Canada, Governor.

TUCSON, ARIZ., Feb. 11. Dr. Leslie R. Kober, 15 East Monroe St., Phoenix, Ariz., Governor.

LINCOLN, NEB., Cornhusker Hotel, Mar. 3. Dr. Edmond M. Walsh, 1412 Medical Arts Bldg., Omaha 2, Neb., Chairman.

SECTIONAL MEETINGS, AMERICAN COLLEGE OF SURGEONS:

PHILADELPHIA, The Bellevue-Stratford, Feb. 13-16. Dr. Calvin M. Smyth Jr., Abington Memorial Hospital, Abington, Pa., Chairman.

MILWAUKEE, Hotel Schroeder, Feb. 27-29. Dr. Forrester Raine, 425 E. Wisconsin Ave., Milwaukee 4, Chairman.

COLORADO SPRINGS, COLO., The Broadmoor, Mar. 5-7. Dr. George W. Bancroft, 106 E. St. Vrain St., Colorado Springs, Colo., Chairman.

LITTLE ROCK, ARK., Hotel Marion, Mar. 12-13. Dr. Joseph F. Shuffield, 103 E. 7th St., Little Rock, Ark., Chairman.

SOCIETY OF UNIVERSITY SURGEONS, Hotel Claypool, Indianapolis, Feb. 8-10. Dr. C. Rollins Hanlon, 1325 South Grand Blvd., St. Louis 4, Secretary.

SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS, Hollywood Beach Hotel, Hollywood, Fla., Jan. 28-Feb. 1. Dr. C. H. Mauzy, Bowman Gray School of Medicine, Winston-Salem, N. C., Secretary.

SOUTHEASTERN SURGICAL CONGRESS, John Marshall Hotel, Richmond, Va., Mar. 12-15. Dr. Benjamin T. Beasley, 701 Hurt Bldg., Atlanta 3, Ga., Secretary.

SOUTHERN SECTION, AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, The Shamrock, Houston, Texas, Jan. 27-28. Dr. J. M. Robison, 1304 Walker Ave., Houston 2, Texas, Chairman.

U. S. SECTION, INTERNATIONAL COLLEGE OF SURGEONS, REGIONAL MEETING, Greenbrier Hotel, White Sulphur Springs, W. Va., Feb. 12-15. Dr. E. G. Gill, 711 South Jefferson St., Roanoke, Va., Chairman.

WESTERN SECTION, AMERICAN FEDERATION FOR CLINICAL RESEARCH, Golden Bough Theater, Carmel, Calif., Jan. 26. Dr. Charles M. Grossman, 301 Selling Bldg., Portland 5, Ore., Secretary.

WESTERN SOCIETY FOR CLINICAL RESEARCH, Carmel-by-the-Sea, Calif., Jan. 27-28. Dr. Arthur J. Seaman, University of Oregon Medical School, Portland 1, Ore., Secretary.

FOREIGN AND INTERNATIONAL

ASSOCIATION OF INDUSTRIAL MEDICAL OFFICERS, London School of Hygiene and Tropical Medicine, London W.C.1, England, Sept. 24-28, 1956. Dr. J. A. A. Mekelburg, Peek, Frean and Company, Ltd., Keetons Rd., Bermondsey, London, S.E.16, England, Honorable Secretary.

BRITISH MEDICAL ASSOCIATION, Brighton, England, July 9-13, 1956. Dr. Angus Macrae, B. M. A. House, Tavistock Square, London, W.C.1, England.

CANADIAN MEDICAL ASSOCIATION, Quebec, P. Q., Canada, June 10-14, 1956. Dr. Arthur D. Kelly, 150 St. George St., Toronto 5, Ont., Canada, Secretary.

CONFERENCE OF INTERNATIONAL UNION FOR HEALTH EDUCATION OF THE PUBLIC, Rome, Italy, April 27-May 5, 1956. Mr. Lucien Viborel, 92 rue St. Denis, Paris 1er, France, Secretary-General.

CONGRESS OF INTERNATIONAL ANESTHESIA RESEARCH SOCIETY, Miami Beach, Fla., U.S.A., April 9-12, 1956. For information write: Dr. R. J. Whitacre, 13951 Terrace Road, Cleveland 12, Ohio, U. S. A.

CONGRESS OF INTERNATIONAL ASSOCIATION OF LIMNOLOGY, Helsinki, Finland, July 26-Aug. 7, 1956. For information address: Dr. H. Luther, Snellmansgatan 16 C 36, Helsinki, Finland.

CONGRESS OF INTERNATIONAL ASSOCIATION OF LOGOPEDICS AND PHONIATRICS, Barcelona, Spain, Sept. 3-7, 1956. Dr. J. Perello, Provenza 319, Barcelona 9, Spain, Secretary-General.

CONGRESS OF INTERNATIONAL SOCIETY OF HEMATOLOGY, Hotel Somerset, Boston, Mass., U.S.A., Aug. 27-Sept. 1, 1956. Dr. W. C. Moloney, 39 Bay State Road, Boston, Mass., U.S.A., Secretary.

CONGRESS OF INTERNATIONAL UNION AGAINST TUBERCULOSIS, New Delhi, India, Jan. 3-6, 1957. For information address: Secretariat, The Union, 66 Boulevard Saint-Michel, Paris 6e, France.

CONGRESS OF LATIN SOCIETY OF OPHTHALMOLOGY, Madrid, Spain, April 24-28, 1956. For information address: Dr. Costi, Montalban 3, Madrid, Spain.

EUROPEAN CONGRESS OF ALLERGOLOGY, Florence, Italy, Sept. 12-15, 1956. Prof. Umberto Serafini, Instituto de Patologia Medica, Viale Morgagni, Florence, Italy, Secretary-General.

EUROPEAN CONGRESS OF CARDIOLOGY, Stockholm, Sweden, Sept. 10-14, 1956. Dr. Karl Erik Grewin, Sodersjukhuset, Stockholm, Sweden, General Secretary.

EUROPEAN SYMPOSIUM ON VITAMIN B_{12}, Hamburg, Germany, May, 1956. For information write: Doz. Dr. H. Bauer, Nervenklinik, Hamburg-Eppendorf, Germany.

HEALTH CONGRESS, ROYAL SOCIETY FOR THE PROMOTION OF HEALTH, Blackpool, England, April 24-27, 1956. Mr. P. Arthur Wells, 90 Buckingham Palace Road, London S.W. 1, England, Secretary.

INTER-AMERICAN CONGRESS OF CARDIOLOGY, Havana, Cuba, Nov. 4-10, 1956. For information address: Dr. Ramon Aixala, Apartado 2108, Havana, Cuba.

INTERNATIONAL ACADEMY OF PATHOLOGY, Cincinnati, Ohio, U. S. A., April 24-25, 1956. Dr. F. K. Mostofi, Armed Forces Institute of Pathology, Washington 25, D. C., U. S. A., Secretary.

INTERNATIONAL CONGRESS AGAINST ALCOHOLISM, Istanbul, Turkey, Sept. 10-15, 1956. For information address: International contre l'Alcoolisme, Case Gare 49, Lausanne, Switzerland.

INTERNATIONAL CONGRESS ON ANIMAL REPRODUCTION, Arts School, University of Cambridge, Cambridge, England, June 25-30, 1956. Dr. Joseph Edwards, Production Division, Milk Marketing Board, Thames Ditton, Surrey, England, Hon. Secretary.

INTERNATIONAL CONGRESS OF ANTHROPOLOGICAL AND ETHNOLOGICAL SCIENCES, Philadelphia, Pa., U. S. A., Sept. 2-9, 1956. Dr. William N. Fenton, National Research Council, Division of Anthropology and Psychology, 2101 Constitution Avenue, Washington 25, D. C., U. S. A., Secretary-General.

INTERNATIONAL CONGRESS OF DIETETICS, Congress Palace, Esposizione Universale Roma, Rome, Italy, Sept. 10-14, 1956. Prof. E. Serianni, Associazione Dietetica, Italiana, via dei Penitenzieri N. 13, Rome, Italy, Secretary General.

INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST, Cologne, Germany, Aug. 19-23, 1956. Mr. Murray Kornfeld, 112 East Chestnut St., Chicago 11, Illinois, U. S. A., Executive Director.

INTERNATIONAL CONGRESS OF ENTOMOLOGY, Montreal, Canada, Aug. 17-25, 1956. Mr. J. A. Downes, Science Service Bldg., Carling Ave., Ottawa, Ont., Canada, Secretary.

INTERNATIONAL CONGRESS OF GASTROENTEROLOGY, London, England, July 18-21, 1956. Mr. Hermon Taylor, London Hospital, White Chapel, London E.1, England, Honorable Secretary.

INTERNATIONAL CONGRESS OF HEALTH TECHNICIANS, Maison de la Mutualite, Paris, France, June 5-8, 1956. For information address: Mr. M. H. Thoillier, 37 Rue de Monthlon, Paris 9e, France.

INTERNATIONAL CONGRESS FOR THE HISTORY OF SCIENCE, Florence and Milan, Italy, Sept. 3-10, 1956. Dr. M. L. Bonelli, Instituto di Ottica, Arcetri, Florence, Italy, Secretary-General.

INTERNATIONAL CONGRESS OF HUMAN GENETICS, Copenhagen, Denmark, Aug. 1-6, 1956. For information address: The University Institute for Human Genetics, Tagensvej 14, Copenhagen N, Denmark.

INTERNATIONAL CONGRESS OF HYDATID DISEASE, Athens, Greece, Sept. 14-18, 1956. Prof. B. Kourias, Croix-Rouge Hellenique, 1 rue Mackenzie King, Athens, Greece, Secretary-General

INTERNATIONAL CONGRESS ON INFECTIOUS PATHOLOGY, Lyon, France, May 24-26, 1956. General Secretariat: Institut Pasteur de Lyon, 77 rue Pasteur, Lyon, France.

INTERNATIONAL CONGRESS OF INTERNAL MEDICINE, Madrid, Spain, Sept. 19-23, 1956. Dr. J. C. De Oya and Dr. J. Gimena, Hostaleza No. 90, Madrid, Spain, Secretaries.

INTERNATIONAL CONGRESS OF INTERNATIONAL COLLEGE OF SURGEONS, Palmer House, Chicago, Illinois, U. S. A., Sept. 9-13, 1956. Dr. Max Thorek, 1516 Lake Shore Drive, Chicago, Illinois, U. S. A., Secretary-General.

INTERNATIONAL CONGRESS OF NEO-HIPPOCRATIC MEDICINE, Montecatini, Terme, Italy, May 20-22, 1956. Dr. Valente, 41 Avenue Verdi, Montecatini Terme, Italy, Secretary-General.

INTERNATIONAL CONGRESS OF PAEDIATRICS, Copenhagen, Denmark, July 22-27, 1956. Professor P. Plum, Rigshospitalet, Copenhagen, Denmark, President.

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, Copenhagen, Denmark, August 20-24, 1956. Dr. B. Strandberg, Kobenhavns amts sygehus i Gentofte, Dept. of Rheumatology and Physical Medicine, Hellerup, Denmark, Honorable Secretary.

INTERNATIONAL CONGRESS OF RADIOLOGY, Mexico, D. F., Mexico, July 22-28, 1956. Dr. Jose Noriega, Tepic 126 (2e piso), Mexico, D. F 7, Mexico, Secretary General.

INTERNATIONAL CONGRESS OF WORLD CONFEDERATION FOR PHYSICAL THERAPY, Hotel Statler, New York, New York, U. S. A., June 17-23, 1956. For information address: Miss Mildred Elson, American Physical Therapy Association, 1790 Broadway, New York 19, New York, U. S. A.

INTERNATIONAL GENETICS SYMPOSIUM, Tokyo and Kyoto, Japan, Sept. 6-12, 1956. For information address: Secretary, International Genetics Symposium, Science Council of Japan, Ueno Park, Tokyo, Japan.

INTERNATIONAL PHYSIOLOGICAL CONGRESS, Brussels, Belgium, July 29-Aug. 5, 1956. For information address: Prof. J. Reuse, Faculte de Medicine et de Pharmacie, 115 Boulevard de Waterloo, Brussels, Belgium.

INTERNATIONAL PROFESSIONAL UNION OF GYNECOLOGISTS AND OBSTETRICIANS, Madrid, Spain, Sept. 28-29, 1956. Dr. Jacques Courtois, 1 rue Racine, St-Germain-en-Laye (S and O), France, Permanent International Secretary-General.

INTERNATIONAL SYMPOSIUM ON VENEREAL DISEASES AND THE TREPONEMATOSES, Hotel Statler, Washington, D. C., U. S. A., May 28-June 1, 1956. For information address: Dr. Charles A. Smith, Chief, Venereal Disease Program, Division of Special Health Services, Public Health Service, Dept. of Health, Education and Welfare, Washington 25, D. C., U. S. A.

LATIN AMERICAN CONGRESS OF PHYSICAL MEDICINE, San Juan, Puerto Rico and Curacao, N.W.I., Jan. 29-Feb. 8, 1956. Dr. Cassius Lopez de Victoria, 176 East 71st St., New York 21, New York, U. S. A., Executive Director.

MEDICAL WOMEN'S INTERNATIONAL ASSOCIATION, EXTRAORDINARY GENERAL ASSEMBLY, Burgenstock, Nidwalden, Switzerland, Sept. 21-23, 1956. Dr. Janet Aitken, 30a Acacia Road, London N.W. 1, England, Secretary.

MIDDLE EAST MEDICAL ASSEMBLY, Campus, American University of Beirut, Beirut, Lebanon, April 7-9, 1956. Dr. Virgil C. Scott, American University of Beirut, Beirut, Lebanon, Chairman.

NATIONAL CONGRESS OF PEDIATRICS, Cuidad Universitaria, Mexico D.F., Mexico, May 1-5, 1956. Dr. Ignacio Avila Cisneros, Calzada de Madereros No. 240, Mexico 18, D.F., Mexico, Coordinator.

NORTH QUEENSLAND MEDICAL CONFERENCE, Cairns, North Queensland, Australia, June 25-30, 1956. Dr. W. R. Horsfall, P. O Box 672, Cairns, N.Q., Australia, Secretary.

PAN-AMERICAN ACADEMY OF GENERAL PRACTICE, San Juan, Puerto Rico and Curacao, N.W.I., Jan. 29-Feb. 8, 1956. Dr. Arturo Martinez, 54 East 72d St., New York 21, New York, U. S. A., Secretary.

PAN AMERICAN CONGRESS ON CANCER CYTOLOGY, Miami, Fla., U. S. A., Jan. 8-12, 1957. Dr. J. Ernest Ayre, 1155 N.W. 14th St., Miami, Fla., U. S. A., General Chairman.

PAN AMERICAN CONGRESS OF GASTROENTEROLOGY, Havana, Cuba, Jan. 20-27, 1956. For information address: Dr. Norberto M. Stapler, 1267 J. E. Uriburu, Buenos Aires, Argentine, S. A.

PAN AMERICAN CONGRESS OF OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY, San Juan, Puerto Rico, April 8-12, 1956. Dr. C. E. Munoz MacCormick, Apartado 9111, Santurce 29, Puerto Rico, Secretary General.

PAN AMERICAN MEDICAL WOMEN'S ALLIANCE, Santiago, Chile, March 6-13, 1956. For information address: Dr. Eva Cutright, 458 Beall Ave., Wooster, Ohio, U. S. A.

WORLD CONGRESS ON FERTILITY AND STERILITY, Naples, Italy, May 18-26, 1956. Dr. Maxwell Roland, 114-20 Queens Boulevard, Forest Hills 75, New York, N. Y., U. S. A., Chairman, Liaison Committee.

WORLD MEDICAL ASSOCIATION, Havana, Cuba, Oct. 9-15, 1956. Dr. Louis H. Bauer, 345 East 46th St., New York 17, New York, U. S. A., Secretary-General.

EXAMINATIONS AND LICENSURE

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Written.* Various locations in the United States and Canada, July 20. Final date for filing application was Jan. 20. *Oral.* Miami Beach, Mar. 18-22. Sec., Dr. C. B. Hickcox, 80 Seymour St., Hartford 15, Conn.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY. *Written.* Various centers, July 26. *Oral.* St. Louis, Oct. 12-15. Final date for filing applications is April 1. Sec., Dr. B. M. Kesten, One Haven Ave., New York 32.

AMERICAN BOARD OF INTERNAL MEDICINE: *Written.* Oct. 15, 1956. Final date for filing application is May 1. *Oral Examinations in 1956.* New Orleans, Feb. 7-10; Los Angeles, April 12-14; Chicago, June 7-9. Final date for filing application for these three oral examinations was Jan. 3. New York City, Sept. 21-25. Final date for filing application is April 1. Exec. Sec., Dr. William A. Werrell, 1 West Main St., Madison 3, Wis.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *Written Examination and submission of Case Reports. Part I.* Various locations in United States and Canada, and military centers outside of the continental United States, Feb. 3, 1956. Final date for filing application was Oct. 1. *Oral and Pathological Examinations. Part II.* Chicago, May 11-20, 1956. Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Written.* January 24-26, 1956. *Practical Examination.* San Francisco, June 18-21, St. Louis, Oct. 20-25. Applications for 1957 written examination must be filed before July 1, 1956. Sec., Dr. Merrill J. King, Box 236, Cape Cottage Branch, Portland 9, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Oral.* Jan. 26-27. Final date for filing application was Aug. 15. *Part I. Oral and written.* Various centers, April, 1956. Final date for filing application was Nov. 30. Sec., Dr. Harold A. Sofield, 116 South Michigan Ave., Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY. *Oral.* Montreal, Canada, May 6-10. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

AMERICAN BOARD OF PHYSICAL MEDICINE AND REHABILITATION. *Parts I and II.* Chicago, June 16-17. Sec., Dr. Earl C. Elkins, 200 First St., S. W., Rochester, Minn.

AMERICAN BOARD OF PLASTIC SURGERY. *Entire Examination.* Buffalo, May 13-15. Final date for filing case reports was Jan. 1. Corres. Sec., Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: New York City, December, Philadelphia, April 16-18, 1956. Sec., Dr. David A. Boyd, 102-110 Second Ave. S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: Atlanta, Ga., Mar. 6-10. Final date for filing application was Dec. 1.; Chicago, June 5-9. Final date for filing applications was Jan. 1.; Los Angeles, Sept. 30-Oct. 4. Final date for filing applications is June 1. Sec., Dr. B. R. Kirklin, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Part I.* Centers throughout the United States, in Europe and in the Far East, March 28. Closing date for the March examination was December 1. Part II. Los Angeles, Feb. 13-14; San Francisco, Feb. 16-17; Durham, March 12-13; Boston, May 14-15 and Philadelphia, June 4-5. Sec., Dr. John B. Flick, 255 S. Fifteenth St., Philadelphia 2.

BOARD OF THORACIC SURGERY. *Written.* February 1956. Closing date for filing application was Dec. 1. Sec., Dr. William M. Tuttle, 1151 Taylor Ave., Detroit 2, Mich.

MAGAZINE–TELEVISION REPORT

The following list of current medical articles in mass-circulation magazines and forthcoming network television programs on medical subjects is published each week only for the information of readers of THE JOURNAL. *Unless specifically stated, the American Medical Association neither approves nor disapproves of the articles and programs reported.*

TELEVISION

Monday, Jan. 30

NBC-TV 11 a. m.–noon EST. "Medical and Health News," a segment of the "Home" show.

ABC-TV, 8:30 p. m. EST. "Medical Horizons" takes up treatment of arthritis in a remote pickup from University of Buffalo School of Medicine, Buffalo, N. Y. Produced in cooperation with the American Medical Association.

MAGAZINES

Pageant, February, 1956

"Who Says You're Crazy?" by Dr. Louis E. Bisch

The author explains "normal deviations within the normal" in an effort to calm people who think they notice symptoms of mental illness.

"They're Still Arguing About Test Tube Babies," by Henry Lee

A summary of recent pronouncements on the subject of artificial insemination, including "official" endorsement of AID—artificial insemination by a donor—by the American Society for the Study of Sterility.

"The Safe Pill That Makes You Feel Good," by Thomas Conway

A semihumorous report on Equanil, Wyeth Laboratories' trade name for the tranquilizing drug, Miltown. The article quotes a *Life* magazine writer who pokes fun at the drug and reports on current research into the product.

"The Big Lie About Moderate Drinking," by William Rambo

What happens to the average man or woman when he or she drinks? The article tells what alcohol does to the human body and concludes with a discussion of hang-over cures.

Coronet, February, 1956

"The Sham of School Health Examinations," by Walter A. Gardell as told to Mary Jacobs

"Medical and educational authorities condemn the situation (regarding school medical examinations) as a national disgrace." The article concludes with this advice: "Abandon the farce of annual examinations" (giving instead more thorough examinations at regular intervals); "organize community forces"; "have parents present at examinations"; "provide adequate facilities"; and "give examining doctors more help."

"What Is a Stroke?" by Lester David

In answer to the question posed in the title, the author explains cerebral hemorrhage and cerebral thrombosis. He also tells why a stroke causes paralysis, how to recognize a stroke victim, and what can be done to prevent the occurrence of paralysis.

"America's Happiest Hospital," by Andrew Hamilton

"Within ten years, without Federal subsidy, state funds, financing by foundations or invested capital, the $10,000,000 City of Hope Hospital, Duarte, California, has become one of America's leading medical centers."

Esquire, February, 1956

"Gadfly of Medicine," by Caroline Bird

The story of the British medical periodical, The *Lancet*, which "reports the world from virus to rocket ship through the doctor's eye."

DEATHS

Orr, Thomas Grover, Kansas City, Kan.; born in Carrollton, Mo., May 9, 1884; Johns Hopkins University School of Medicine, Baltimore, 1910; since 1954 professor emeritus of surgery, University of Kansas School of Medicine, where he joined the faculty in 1914, serving as instructor in surgery until 1917, when he became associate professor of surgery, and from 1924 to 1949 professor of surgery and chairman of the department; member of the founders group of the American Board of Surgery; past-president of the American Surgical Association, Western Surgical Association, Kansas City Academy of Medicine, Kansas City Surgical Society, Kansas City Southwest Clinical Society, and the Southwestern Surgical Congress; member of the American Society of the History of Medicine, Southeastern Surgical Congress, Chicago Surgical Society, Society of University Surgeons, Societé Internationale de Chirurgie, Central Surgical Association, Sigma Xi, Alpha Omega Alpha, Nu Sigma Nu, and Beta Theta Pi; fellow of the American College of Surgeons, of which he was a member of the board of governors; during World War I a major in the Medical Corps of the U. S. Army; on June 8, 1955, received an honorary doctor of science degree from the University of Missouri, Columbia; editor of *American Surgeon;* editor-in-chief of *Survey of Surgical Techniques;* on the editorial boards of *Surgery, Quarterly Review of Surgery,* and *International Record of Medicine*; author of "Modern Methods of Amputation" and "Operation of General Surgery"; consultant in surgery to the Veterans Administration Hospital in Kansas City, Mo.; on the staff of the University of Kansas Medical Center, where he died Nov. 19, aged 71, of myocardial infarction.

Brooks, Paul Bellows, Montgomery, N. Y.; born in Norwich in 1878; University and Bellevue Hospital Medical College, New York City, 1903; after internship at Bellevue Hospital served at the Buffalo State Hospital for the Insane from 1905 to 1907; was a general practitioner at Norwich from 1907 to 1915, when he joined the state health department as district health officer; in 1917 became acting director of the division of communicable diseases, and was assistant director of the division of laboratories and research from 1919 to 1923, when he became deputy health commissioner; retired Jan. 1, 1946; member of the state board of medical examiners and of the U. S. Public Health Service Sanitation Advisory Board; president of the International Association of Milk Sanitarians in 1939-1940 and at one time secretary-treasurer; member of the Alumni Society of Bellevue Hospital, American Public Health Association, and the New York State Association of Public Health Laboratories; for one year secretary of the health officers section of the American Public Health Association and president of the New York State Association of Dairy and Milk Inspectors; for four years chairman of the public health section of the Medical Society of the State of New York; associate member of the American Medical Association; for many years secretary of the Chenango County Medical Society; for many years author of "Doctor Jones Says" column, which appeared in the health department bulletin and in many newspapers; served as associate editor of the *Journal of Milk Technology;* died in Middletown Nov. 19, aged 77.

Akelaitis, Andrew John Edward, New York City; born in Baltimore July 11, 1904; Johns Hopkins University School of Medicine, Baltimore, 1929; assistant professor of clinical medicine (neurology) at Cornell University Medical College; formerly on the faculty of University of Rochester School of Medicine and Dentistry; specialist certified by the American Board of Psychiatry and Neurology; fellow of the American Psychiatric Association; member of the New York Society for Clinical Psychiatry and the New York Neurological Society; served during World War II; formerly on the staffs of the Strong Memorial and Monroe County hospitals in Rochester, N. Y.; served as attending neuropsychiatrist, Mount Vernon (N. Y.) Hospital; on the staff of the Bellevue Hospital and the New York Hospital, where he died Nov. 24, aged 51.

Aragona, Anthony John ⊕ Lake Success, N. Y.; Université de Lausanne Faculté de Médecine, Switzerland, 1943; served on the staff of the Mary Immaculate Hospital in Jamaica; died Nov. 17, aged 40, of myocardial infarction.

Ayvazian, Haig A., Flushing, N. Y.; American University of Beirut School of Medicine, Syria, 1912; formerly practiced in New York City, where he was on the staff of the French Hospital; died in the University Hospital, New York City, Nov. 26, aged 69, of pancreatitis.

Biedermann-Boehm, Rosella Louise, Bluffton, Ohio; Woman's Medical College of Pennsylvania, Philadelphia, 1923; certified by the National Board of Medical Examiners; died in the Blanchard Valley Hospital in Findlay Nov. 8, aged 58, of cancer.

Bookwalter, Harry ⊕ Columbiana, Ohio; University of Wooster Medical Department, Cleveland, 1900; also a graduate in pharmacy; past-president of the Columbiana County Medical Society; past-president of the Columbiana County Board of Health; vice-president of the Union Banking Company, of which he was past-president; formerly mayor; past-chief of staff at Salem City Hospital in Salem, where he died Nov. 13, aged 83, of chronic pancreatitis.

Buffum, Erwin W., East Aurora, N. Y.; University of Buffalo School of Medicine, 1891; an associate member of the American Medical Association; for many years school physician in East Aurora and health officer for the town of Aurora; died in the Buffalo (N. Y.) General Hospital Oct. 27, aged 89.

Caccamise, Charles William ⊕ Rochester, N. Y.; University of Buffalo School of Medicine, 1918; for many years senior medical examiner, New York State Compensation Commission; on the staff of the Park Avenue Hospital; past-president of the University of Buffalo Alumni Association; died in the Strong Memorial Hospital Nov. 21, aged 61, of bronchopneumonia and metastatic brain tumor.

Carroll, John Dennis ⊕ Troy, N. Y.; Albany (N. Y.) Medical College, 1916; past-president of the Rensselaer County Medical Society; served during World War I; on the staff of St. Mary's Hospital, where he died Nov. 9, aged 62, of adenocarcinoma of the common bile duct.

Colvin, Paul Verlander, Longview, Texas; Tulane University of Louisiana School of Medicine, New Orleans, 1931; member of the State Medical Association of Texas; served during World War II and was awarded the American Theater ribbon, Victory medal, and American Defense ribbon; died in Ruston, La., Nov. 2, aged 51, of carcinoma of the liver.

Creighton, Ralph Higby ⊕ Minneapolis; University of Minnesota Medical School, Minneapolis, 1924; member of the Minnesota State Medical Association and the American Academy of General Practice; past-president of the Hennepin County Medical Society, of which he was a member of the board of directors; served during World War II; chief of staff of the Abbott Hospital; on the staff of the Asbury Methodist Hospital; died Nov. 11, aged 57, of coronary thrombosis.

Davis, Thomas Wallis, Utica, N. Y.; Cornell University Medical College, New York City, 1919; member of the Industrial Medical Association; fellow of the American College of Surgeons and the New York Academy of Medicine; served during World War I; formerly on the staffs of the Hospital for Special Surgery, St. Clare's Hospital, and the Midtown Hospital in New York City, where for many years he was medical director of the Borden Company; died in the New York Hospital, New York City, Nov. 23, aged 64.

Friddell, William F. ⊕ Boston, Ga.; Southern Medical College, Atlanta, 1892; died Oct. 9, aged 86, of chronic nephritis.

⊕ Indicates Member of the American Medical Association.

Fuld, M. Ernst, New York City; Kaiser-Wilhelms-Universität Medizinische Fakultät, Strassburg, Germany, 1896; an associate member of the American Medical Association; died Nov. 30, aged 82, of myocardial infarction.

Gill, Americus Mack ⊕ Sidon, Miss.; Medical Department of Tulane University of Louisiana, New Orleans, 1909; died Nov. 8, aged 79, of coronary thrombosis.

Glasgow, Maude, New York City; Cornell University Medical College, New York City, 1901; an associate member of the American Medical Association; formerly a medical examiner for the city health department and the school board; at one time chief women's physician for the New York Telephone Company; served on the staff of the New York Infirmary; author of "Life and Law" and other books; died Nov. 20, aged 87, of coronary thrombosis.

Grad, Herman, Woodmere, N. Y.; University of the City of New York Medical Department, 1894; an associate member of the American Medical Association; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the American College of Surgeons; consultant at Long Beach (N. Y.) Hospital, St. Joseph's Hospital, Far Rockaway, and the Woman's Hospital in New York City; died Nov. 7, aged 83, of arteriosclerosis.

Green, William Louis ⊕ Pekin, Ind.; Western Reserve University Medical Department, Cleveland, 1900; for many years president of the school board and director of the Citizens Bank; on the staff of the Washington County Memorial Hospital in Salem; physician and surgeon for the Monon Railroad; during World War I was a member of the draft board and examining physician in the county for the armed forces; during World War II served as examining physician; died Oct. 25, aged 81, of coronary disease.

Greist, Henry Wireman ⊕ Monticello, Ind.; Medical College of Indiana, Indianapolis, 1894; for many years a medical missionary in Alaska; died Nov. 9, aged 87, of coronary thrombosis.

Hadley, Murray Nathan ⊕ Indianapolis; Medical College of Indiana, Indianapolis, 1903; associate professor emeritus of surgery at the Indiana University School of Medicine; fellow of the American College of Surgeons; member of the founders group of the American Board of Surgery; past-president of the Indianapolis Medical Society; on the staffs of St. Vincent's and Indianapolis General hospitals and the Methodist Hospital, where he died Nov. 3, aged 81, of cerebral hemorrhage and arteriosclerotic heart disease.

Halligan, Raymond S. ⊕ Flint, Mich.; Saginaw (Mich.) Valley Medical College, 1903; on the staffs of the Hurley and McLaren hospitals and St. Joseph's Hospital, where he died Nov. 15, aged 76, of ruptured arteriosclerotic abdominal aortic aneurysm.

Haury, Victor Givens ⊕ Wellsville, Kan.; University of Minnesota Medical School, Minneapolis, 1935; member of the American Academy of General Practice; at one time on the faculty of Jefferson Medical College in Philadelphia; on the staff of the Bethany Hospital, Kansas City, where he died Nov. 11, aged 50, of pyelonephritis.

Hearn, Arthur Joseph, White Plains, N. Y.; Johns Hopkins University School of Medicine, Baltimore, 1920; formerly on the staff of St. Agnes Hospital; on the staff of the Lawrence Hospital in Bronxville; died Nov. 13, aged 60.

Hope, James Alexander, Golden City, Mo.; St. Louis College of Physicians and Surgeons, 1889; died Sept. 20, aged 92, of cerebral hemorrhage.

Huth, Lucia Clara Hoyer, Bonita Springs, Fla.; Woman's Medical College of Baltimore, 1908; died in the Lee Memorial Hospital, Fort Myers, Oct. 6, aged 69, of coronary thrombosis.

Jacobstein, Harry ⊕ Mount Vernon, N. Y.; University and Bellevue Hospital Medical College, New York City, 1911; on the staffs of the Hebrew Home and Hospital for Chronic Sick and the Lebanon Hospital in New York City; died Nov. 7, aged 68, of acute coronary occlusion.

Killips, Thomas Allen, Lyons, N. Y.; Jefferson Medical College of Philadelphia, 1908; served as mayor of Lyons; died Dec. 5, aged 75.

Kohrman, Benjamin Myron ⊕ Michigan City, Ind.; Ohio State University College of Medicine, Columbus, 1933; fellow of the International College of Surgeons, American Association of Railway Surgeons, and the American College of Surgeons; on the staff of the Doctors Hospital, where he died Nov. 26, aged 46, of reticulum cell sarcoma.

Leiker, Raymond Joseph ⊕ Great Bend, Kan.; St. Louis University School of Medicine, 1929; served during World War II; died Nov. 21, aged 51, of acute coronary occlusion.

Lipscomb, Lee McDonald ⊕ Jackson, Miss.; Northwestern University Medical School, Chicago, 1934; certified by the National Board of Medical Examiners; interned at the Los Angeles County General Hospital; served during World War II; on the staffs of the Veterans Administration, Baptist, and St. Dominic's hospitals; died Nov. 22, aged 46, of a heart attack.

Luse, Raymond J., Angola, Ind.; Drake University College of Medicine, Des Moines, Iowa, 1906; died in the Logansport (Ind.) State Hospital Sept. 26, aged 75, of bronchopneumonia and arteriosclerotic heart disease.

Miller, Bert Elby ⊕ Council Grove, Kan.; University Medical College of Kansas City, Mo., 1905; president of the Morris County Medical Society; chief of staff, Morris County Hospital, where he died Nov. 26, aged 75, of cerebral vascular accident.

Paige, Beryl Holmes, Amherst, Mass.; Columbia University College of Physicians and Surgeons, New York City, 1924; formerly on the faculty of his alma mater; member of the American Association of Pathologists and Bacteriologists; died in Northampton Oct. 3, aged 65, of arteriosclerotic heart disease.

Parker, Ashley Stephens ⊕ Merced, Calif.; Medical Department of Tulane University of Louisiana, New Orleans, 1893; died in Mercy Hospital Nov. 21, aged 84.

Peck, Raymond Edward ⊕ Davenport, Iowa; State University of Iowa College of Homeopathic Medicine, Iowa City, 1897; served on the faculty of his alma mater; past-president of the Scott County Medical Society and vice-president of the Iowa State Medical Society; served during World War I; died in St. Luke's Hospital Nov. 26, aged 78, of cerebral hemorrhage.

Perry, Henry B. ⊕ Boone, N. C.; North Carolina Medical College, Davidson, 1905; state senator; died in the Wesley Long Hospital, Greensboro, Nov. 19, aged 76, of carcinoma of the prostate.

Petty, Alonzo Allen, Homestead, Fla.; Indiana University School of Medicine, Indianapolis, 1929; died in the James Archer Smith Hospital Oct. 23, aged 67, of cerebral vascular accident and hypertension.

Risk, Robert Alexander, Muskegon, Mich.; Detroit College of Medicine, 1904; served as county coroner; on the staffs of the Hackley and Mercy hospitals; died Nov. 23, aged 74, of acute cardiac dilatation and arteriosclerosis.

Sankey, Joseph Malloy, Hatchechubbee, Ala.; Medical College of Alabama, Mobile, 1904; died in the Veterans Administration Hospital, Tuscaloosa, Sept. 30, aged 76, of bilateral bronchopneumonia.

Wheeler, Alonzo Marsh ⊕ Berrien Springs, Mich.; Rush Medical College, Chicago, 1897; member of the Illinois State Medical Society; served on the staff of the West Suburban Hospital in Oak Park, Ill.; died in Niles Nov. 24, aged 84, of injuries received in an automobile accident.

Wood, Will Lee, New Smyrna Beach, Fla.; Emory University (Ga.) School of Medicine, 1914; an associate member of the American Medical Association; died Oct. 8, aged 66, of multiple liver abscesses and chronic cholecystitis.

Wright, Floyd Robbins, Townsend, Del.; Cornell University Medical College, New York City, 1903; fellow of the American College of Physicians; formerly on the faculty of the Ithaca division of his alma mater; died Oct. 25, aged 81, of cancer and pernicious anemia.

FOREIGN LETTERS

BRAZIL

Extrahepatic Biliary Lesions.—Dr. R. P. Albuquerque (*Rev. brasil. cir.* **30**:249, 1955) reported on a series of 210 patients with biliary tract lesions, some of whom were operated on more than once. Only one patient in this series died. Direct cholecystectomy was performed on 45, retrograde cholecystectomy on 162, and subserous cholecystectomy on 3. In these patients, Kehr's external choledochostomy was performed on 21, repeated choledochostomy on 2, and cholecystogastrotomy on 2. As a supplementary operation, appendectomy was performed on 26, umbilical herniorrhaphy on 2, unilateral oophorectomy on one, and myomectomy on one. Biliary surgery aims to correct the anatomic and functional changes of the distal portion of the bile duct. The era of pure cholecystectomy, which does not consider the dynamic modification of the biliary canal, has given way to the surgery of the common bile duct. It is this duct that should interest the conscientious surgeon, because only here can he obtain the most permanent results. The sequelae of cholecystectomy are at times more troublesome than the initial symptoms. The surgeon must find a way to understand better the true causative mechanism of the biliary hypertonia syndrome connected with gallbladder changes in order to be able to correct them surgically.

Epidemic Typhus.—Dr. J. Alves Meira and his co-workers (*Rev. Hosp. clín.* **10**:237, 1955) describe what seems to be the first reported case of epidemic typhus in South America. Because the disease is rare in Brazil, the diagnosis is likely to be missed. On the other hand, the great number of emigrants from areas where epidemic typhus is common makes a knowledge of the disease essential for South American physicians. The patient, a 21-year-old Russian man, was admitted to the hospital, with a high fever, chills, headache, generalized aching pains, nausea, vomiting, and prostration of seven days' duration. A maculopapular rash was present on the thorax and extremities, and his spleen was slightly enlarged. While in Germany in 1945, he had had a severe attack of what was probably typhus during an epidemic. His present attack was treated with chloramphenicol, and he recovered rapidly. The diagnosis was established by serologic studies, with the cooperation of the Rocky Mountain Laboratory, Hamilton, Mont. The authors stress that high fever, resistant to common antipyretics and large doses of penicillin, intense and persistent headache, and a maculopapular rash constitute the most important findings on which to base a tentative diagnosis.

Pyloric Stenosis.—In *Revista paulista de medicina* (**47**:288, 1955) Dr. Arrigo Raia and his co-workers reported the histological changes of the musculature and myenteric plexus of the pyloric antrum of infants, adolescents, and adults with pyloric stenosis. They found that (1) muscular hypertrophy is commoner in infants than in adults with this condition; (2) abnormalities of the myenteric plexus are present in both infants and adults but are much more marked in adults; and (3) the myenteric alterations are reversible in infants and irreversible in adults. Because of the reversibility of the lesions of the myenteric plexus in infants, some cases are spontaneously cured, some are cured by medical measures, and some by operation. The method used in treating infants must maintain the metabolism long enough to permit the myenteric plexus to return to normal. Surgical treatment is preferred. For adults, the only treatment that gives good results is operation, since the myenteric lesions are irreversible.

Postoperative Care.—In *Revista brasileira de cirurgia* (**29**:339, 1955) Dr. Fernando Paulino states that 200 patients subjected to major operations, mostly on the upper gastrointestinal tract, received postoperatively an average of 8 liters of a solution containing dextrose, amino acids, alcohol, electrolytes, and vitamins. No undesirable reactions were observed. This solution provides about 1,000 calories per liter. Thus, sufficient calories can be provided without overhydration of the patient. The author believes that positive nitrogen balance can be maintained by parenteral therapy alone. The intravenous use of alcohol did not interfere with the water balance, sodium and potassium balance, or nonprotein nitrogen levels. Glycosuria seldom occurred, but, when it did, it was corrected by reducing the speed of injection.

ENGLAND

Control of Hospital Cross Infection.—Dr. Leonard Colebrook, late director of the Medical Research Council Burns Unit at Birmingham, in a lecture given in New Zealand, deprecated the complacency with which cross infection in hospitals and operating rooms is tolerated in Great Britain. He considers the irreducible minimum that every conscientious physician and surgeon should wish for has not been approached. He considers that antibiotics should form the second line of defense if the front line against infection fails. The front line should be concerned with preventing the spread of infection. Hospital personnel should diminish the amount of contaminated dust in the wards and prevent its dispersal by air currents. The greater part of the dust comes from bedding, especially sheets and blankets. Because of the risk of shrinkage and felting, the latter are never adequately sterilized nor are they washed more often than is necessary. Oiling blankets minimizes the spread of fluff, but the ideal blanket should be made of sterilizable material. Terylene has been suggested, and blankets made of this material are now on trial in British hospitals. Continuous-flow aerosols of antiseptics such as hexylresorcinol have been installed in over 50 hospitals to control flies, which are important sources of infection. Methods of removing dust from the wards could be improved. Built-in suction systems should be put in all hospitals to avoid raising dust. Soiled bed linen should be placed immediately in closed containers to prevent the spread of infection. Hospital ventilation is imperfect. Few surgeons have any idea whether the air of the operating room is clean at the beginning of an operation or to what extent it is polluted during an operation on an infected patient.

For years burns have been dressed in the burns unit in air containing one or less microbe-carrying particle per cubic foot of air. This is achieved by leading in at ceiling level warm, filtered air under slight positive pressure. All particles are thus swept to the floor, whence they are sucked out of the room by a fan. All wounds should be dressed in properly ventilated dressing rooms and not in open wards. Infected or infective patients should be isolated in separate cubicles or rooms. Another matter in ward routine that needs attention is the sterilization of feeding utensils, bedpans, basins, and baths. The author suggests having a central sterile supply department for the issue of such things as syringes, saline solution, distilled water, and dressings, as is found in some American hospitals, and the appointment of an "infection control officer," whose function would be to direct and coordinate all the activities that make for safety from infection. He should, for example, see that blankets, gloves, and dressings are adequately sterilized; that sterilizers are working properly; that floors, surgeons' shoes, and anesthetists' equipment are suitably disinfected; and that the throats and noses of all medical and nursing personnel are periodically examined. He would also be authorized to make immediate inquiry when any instance of hospital infection occurred.

The items in these letters are contributed by regular correspondents in the various foreign countries.

Munchausen Syndrome.—Several physicians have described what is becoming known as the Munchausen syndrome, named after Baron Munchausen who described fabulous stories of events and journeys that never took place. The syndrome refers to patients who have nothing wrong with them but invent signs and symptoms, going from hospital to hospital asking for treatment. This sometimes includes operative treatment, some of them bearing laparotomy scars. Those inviting such operations are often mentally ill. The condition is distinct from malingering. Gawn and Kauffmann of St. Stephen's Hospital, London, in a communication to the *British Medical Journal,* described a patient brought into the casualty department because of a suspected skull fracture. The patient was found lying in the street apparently bleeding from the ears. His history was that he had had meningitis at the age of 8 years, bleeding from the ears and nose at 10 years, which had continued ever since, and swelling of the left hypochondrium at 18 years. A splenectomy was performed in Dublin, and during convalescence the patient claimed to have had hematuria. Purpura was diagnosed. The patient came to London and was seen at St. Stephen's Hospital. The only abnormal findings were subjective right renal tenderness and blood around the ears and nose, with no visible bleeding point. Complete hematological examination, including bone marrow biopsy and lumbar puncture, showed no abnormality. The patient was found wandering about the hospital smeared with blood. Kept under close observation, he failed to produce any physical signs. Subsequent inquiries revealed that he had had an appendectomy in Paris and by the age of 18 years had visited 31 hospitals in various parts of the British Isles. He simulated bleeding from the nose and ears by scratching and hematuria by soaking small pieces of blood-stained absorbent cotton in his urine. The cost to the National Health Service must have been great. Several other physicians recognized the patient and wrote to the *British Medical Journal* about him. One had seen him in the Western Infirmary, Glasgow, another in the Midlands, and another in Kent, all within a few days. One, who claims that the patient scarified his urethra to produce hematuria, got rid of him by ordering a cystoscopy. A Dublin physician wrote in to say that he had seen the "Baron," as he was known in Dublin, and that he had seven references in the literature to his credit. This physician listed a further 27 hospitals to which the patient had been admitted. A physician from St. Thomas' Hospital, London, claimed that this patient had visited the hospital twice recently with similar hemorrhagic manifestations. As before, the threat of catheterization or cystoscopy resulted in his voluntary discharge. Yet another physician stated that he saw the patient in Newcastle. The suggestion has been made that the *British Medical Journal* publish a "rogues' gallery" of such persons for the protection of physicians, hospitals, and public funds.

Fellowship for Freedom in Medicine.—The annual meeting of the Fellowship for Freedom in Medicine was held in London in November. Tributes were paid to the memory of Lord Horder, who was its founder and former leader. The meeting condemned the discrimination by the state against those members of the public who choose to receive their treatment privately, outside the National Health Service. They are denied drugs and appliances on the same terms as National Health Service patients. The meeting urged the Minister of Health to remedy this injustice without delay. A subcommittee had investigated possible methods of remuneration that could exist side by side as alternatives to the present capitation fee method and enable patients to establish private contractual relationships with their physicians without bearing the whole cost themselves. At present, private practice is all or none. The meeting was impressed by the advantages of the Australian system under which the state assisted the patient to make his own contract for his medical needs. The more private patients there were, the less medical treatment cost the state. A certain number of patients went to state hospitals and physicians because they did not wish to pay twice for their drugs, once through national insurance and again to the pharmacist.

Dr. A. H. Douthwaite moved a resolution urging the Home Secretary to reverse his decision prohibiting the manufacture of heroin for medical purposes. It was considered that heroin was of great value in the treatment of some medical conditions and that the ban on its manufacture would serve no useful purpose. The impression given in the House of Lords was that the medical profession in Britain approved of the ban. The reverse is the case. The final resolution concerned the government inquiry into the number of physicians required in the future. If there should be any move to restrict the freedom of any man or woman to enter the field of medical study, the executive committee of the fellowship should take appropriate action. Government control over the entry of medical students would mean arbitrary alteration of standards by government decree and would rapidly lead to a full-time state-salaried service. It was stated that the fellowship is the only nonpolitical medical body that has the courage and knowledge to criticize the defects of the National Health Service and that the British Medical Association is not a properly critical body because it must be too intimately associated with the Ministry of Health. At present, medicine is in the grip of party politics.

Prednisone and Prednisolone.—Dr. J. Nabarro and his coworkers (*Lancet* **2**:993, 1955) noted clinical effects of prednisone in doses of 30 to 40 mg. daily in five patients with lymphocytic leukemia, two with lymphoma, and one with Schönlein-Henoch disease. Metabolic studies were also made on some of these patients. Those patients that had formerly improved when treated with cortisone maintained their improvement when prednisone was substituted. The therapeutic activity of prednisone is about five times that of cortisone. Studies of glucocorticoid activity in adrenalectomized subjects showed increased nitrogen excretion but little effect on blood sugar. Two patients developed steroid diabetes during treatment with prednisone. The sodium-retaining activity of prednisone was not increased in the same way as the therapeutic and glucocorticoid activities. Most patients treated with 30 to 40 mg. of prednisone daily were able to take a normal amount of sodium in their food. Prednisone caused suppression of adrenocortical activity and most of the other and more serious complications of steroid therapy. Dr. Dudley Hart and his co-workers (*Lancet* **2**:998, 1955) studied the effect of prednisone and prednisolone in a group of 14 patients with rheumatoid arthritis. With one-quarter to one-fifth of the dose of cortisone, these steroids produced symptomatic relief in this condition. All patients had previously been treated with cortisone, which gave them relief. Assessment was made by the patients' own estimation of pain and stiffness, swelling of the finger, joint tenderness, power of the grip, simple function tests, and sedimentation rate. The length of treatment with prednisone or prednisolone lasted from a few weeks to three months. The general impression obtained was that the new steroids gave better relief and acted more rapidly than cortisone. General improvement took place in 10 of the 14 patients on transferring from cortisone to prednisone or prednisolone, but the condition of 8 of these deteriorated somewhat on returning to therapy with cortisone. No toxic effects such as occur after administration of cortisone were noted.

A New Antibiotic.—Professor Gause, deputy director of the Institute for Antibiotic Research of the Academy of Medical Sciences, Soviet Union, has announced in the *British Medical Journal* of Nov. 12, page 1177, the discovery of a new antibiotic, albomycin, which is a cyclopeptide containing amino acids and 4.16% of iron, which suggests that it might interfere with enzyme systems containing iron and transporting oxygen. It was obtained from a new species of Streptomyces, Actinomyces subtropicus, and it inhibits the growth of gram-positive cocci, chiefly pneumococci and micrococci, and, what is more important, the growth of micrococci resistant to other antibiotics such as penicillin, streptomycin, the tetracyclines, and erythromycin. It is also effective against a number of gram-positive bacteria such as the coli-dysentery group and Klebsiella pneumoniae. Albomycin is active at the extreme dilution of 1 in

700 millions (for penicillin the dilution is 1 in 80 millions). Removal of the iron destroys much of its atcivity. The antibiotic inhibits sensitive bacteria only in the presence of oxygen. Like penicillin, albomycin has a low toxicity. Pharmacologically it is inert, and it can be given with safety intrathecally. In experiments on mice infected with 500,000 lethal doses of pneumococci, a survival rate of 100% was obtained with a single subcutaneous injection of 750,000 units of albomycin per kilogram of body weight. In parallel experiments with penicillin, only 20% survived. Albomycin has been found to be inactive against Mycobacterium tuberculosis, Salmonella organisms, and Rickettsia organisms. In combination with penicillin and streptomycin it is synergistic. Clinically albomycin has been used mainly in the treatment of various infections caused by pathogenic cocci and by penicillin-resistant organisms. Intrathecally it has been used in the treatment of meningitis caused by penicillin-resistant organisms.

Somatotypes in Diabetes.—Lister and Tanner have made anthropometric measurements and somatotype photographs of 155 diabetic patients (40 men and 115 women) ranging in age from 16 to 76 years (*Lancet* **2**:1003, 1955). The preponderance of women was due to the fact that most of the patients in one of the hospitals were women. They were divided into two groups by the clinical criteria of acute or nonacute onset of the disease. Patients were somatotyped by inspection of the photographs and the use of Sheldon's tables of height and weight. Measurements of the thickness of a fold of skin were taken halfway down the front of the arm over the biceps; halfway down the back of the arm over the triceps; under the angle of the left scapula; and above the left iliac crest in the anterior axillary line. The logarithm of the sum of the readings was used as a measurement of the amount of body fat. Those patients in whom the onset of diabetes was gradual were more endomorphic and less ectomorphic than those in whom the onset of the disease was acute. Diabetes of acute onset generally appeared at an earlier age. Patients in whom the onset of disease was gradual had more subcutaneous fat and weighed more, despite being not so tall. The highly endomorphic patients were mostly insulin-sensitive. The authors suggest that inherited endomorphy affects the expression of the gene or genes for diabetes of insidious onset, the interaction being physiological. If a person has this gene or genes, the higher the endomorphy the more likelihood there is of diabetes occurring, but, by limiting as much as possible the increase of fat associated with the degree of endomorphy, the chances of manifesting the disease might be reduced.

Cuts in National Health Service.—Drastic proposals to streamline the finances of the National Health Service and to free it from much of the present bureaucratic control are to be recommended to Parliament. Owing to mounting costs these proposals are almost sure to be accepted, in spite of probable objections of the Socialists. These plans follow an inquiry into the finances of the health service ordered by the Minister of Health two and a half years ago. A committee was then set up under the chairmanship of Mr. C. V. Guillebaud. After hearing evidence from various sources the committee has recommended that the charge to patients of 14 cents for a prescription (less than 25% of the cost to the government) be increased; that control of the health service be largely taken from ministry officials and given to the regional boards—hospital management committees would then have more control over their own affairs; and that much of the bureaucratic control of physicians, pharmacists, drug manufacturers, and medical ancillary personnel be cut—physicians should be relieved of much of the useless paper work done at present so that they can devote more time to treating patients. In the opinion of the Guillebaud committee there should be greater emphasis on preventive medicine. Most of the money spent on the health service is on treatment and not prevention. In the hospitals worn-out and obsolete equipment should be replaced and more facilities granted to patients who wish to be treated privately. At the moment private beds in hospital are a luxury. Much public money is spent on welfare foods such as vitamins and cod liver oil. The necessity for this should be reviewed.

Domiciliary Consultations by Specialists.—Hitherto only part-time specialists in the health service have been paid for visits to the patient's home at the request of the general practitioner to advise on the diagnosis and treatment of a patient who cannot be admitted to the hospital. The Minister of Health has now approved of full-time specialists being paid for such visits. Some visits, although made to the patient's home, do not fall within the required category. These include visits to review the urgency of a proposed admission to the hospital or to continue treatment initiated at a hospital, visits made by chest physicians to patients on their clinic register, and visits undertaken as part of work done for a local health officer. Another limitation is that full-time specialists will not be paid for the first eight domiciliary visits made in any three-month period. The fee for both full-time and part-time specialists will be $11.75, with an additional $5.88 if any operative procedure, other than obstetric, is provided or if the specialist uses his own electrocardiograph or portable radiograph; an additional $11.75 will be paid for any obstetric procedure. If a specialist sees more than one patient in the same residence during the same visit the consultation fee will be $5.88 for each patient after the first, and the maximum will be $29.40 however many are seen. Part-time specialists only will receive additional travel payments of $2.94 for a journey of 20 to 40 miles, $5.88 for 40 to 60 miles, and so on, with an extra $2.94 for every 20 miles. The maximum remuneration for domiciliary visits (excluding travel allowance) is $588 in any three months, or $2,352 a year, whichever the specialist prefers.

Chinese Eggs and Food Poisoning.—Most of the outbreaks of paratyphoid reported in the last 10 years have been associated with the consumption of artificial cream used in the preparation of cookies and similar foodstuffs. In outbreaks of typhoid fever infection can often be traced to a carrier, but, in the case of paratyphoid, asymptomatic carriers or patients with mild atypical attacks are usually the immediate source of infection, and they are all the more dangerous when employed in handling food. Meat is sterilized by heating, but many other foodstuffs infected by carriers are eaten without being cooked. Between August and December, 1954, strains of Salmonella schottmülleri phage type 3a var. 2 were identified at the Central Enteric Reference Laboratory, London. This helped Dr. Newell of the Central Public Health Laboratory to track down in widely separated districts six localized outbreaks of paratyphoid associated with cream cookies made by six bakeries (*Month. Bull. Min. Health* **14**:146, 1955). No carriers were found among the food handlers, but it was noted that every bakery used a particular batch of Chinese frozen eggs that were infected. Another outbreak of paratyphoid occurred in August, and bakery products were again suspected. A batch of Chinese frozen eggs appeared on epidemiological grounds to be the source of infection. Newell and his co-workers isolated the same phage type from unused cans of the eggs, from some of the bakery staff, and from some of the patients and their contacts (*Brit. M. J.* **2**:1296, 1955). Two other types of S. schottmülleri and Salmonella thompson were recovered from some other cans of Chinese frozen eggs.

Rockefeller Grants.—Two grants have been made by the Rockefeller Foundation to support research on the structure of protein molecules. The work is being done in collaboration at the Cavendish Laboratory at Cambridge University and the Davy Faraday Research Laboratory of the Royal Institution. For the work at the Cavendish Laboratory, headed by Dr. M. Perutz, the foundation has granted $40,000 over a four-year period; $30,300 for a period of three years has been awarded to the team at the Davy Faraday Research Laboratory led by Sir Lawrance Bragg. The research includes the study of the hemoglobin molecule and the structure of myoglobulin and the nucleic acids by roentgen crystallography and similar techniques. Another Rockefeller Foundation grant of $12,900 is for the purchase of equipment for research on protein metabolism and enzyme action being carried out by Dr. Neuberger at St. Mary's Hospital Medical School,

London. Dr. Neuberger and his group are continuing their long-term studies on the structure and metabolism of the proteins, particularly those of connective tissue, using tissue culture and isotope techniques. Another project is on the metabolism of the porphyrins. A grant of $5,400 has also been made to the University of Oxford for research in crystallography under the direction of Dr. Dorothy Hodgkin, who helped to elucidate the structure of insulin and vitamin B_{12}.

Mitral Valvotomy.—The *British Medical Journal* of Oct. 22 contains a symposium by Baker, Brock, and Campbell based on the results of mitral valvotomy in 45 patients three or more years after operation. At the end of one year 38 patients had good results, at the end of two years 35, and at the end of three years 29, the others having deteriorated or died. The authors concluded that (1) auricular fibrillation does not militate against a successful result and that the state of the valve is much more important than the rhythm, (2) pulmonary hypertension can be expected to be reduced to about half the former level, the fall occurring gradually over many months, (3) the size of the heart does not seem to influence the result, and, although it may decrease, it often does not change, (4) recurrent or continued rheumatic activity may lead to the valve's becoming stenosed again, and (5) although recurrence of the stenosis is rare, a second operation may be indicated.

Mental Health Exhibit.—The Ministers of Labor, of National Service, and of Health opened a mental health exhibit in November, with the twofold object of dispelling the public's fears and misconceptions of mental illness and mental deficiency and of improving the recruitment of nurses in mental hospitals. After a week in London the exhibit went on tour. It included a photographic display to illustrate the nature of mental illness and its treatment and nursing; specialized apparatus, such as the electroencephalograph; models of new proposed mental hospitals; demonstrations of nursing techniques and equipment; and a number of drawings and paintings by mental patients. Since 1948, partly by reallocation of beds and partly by providing new ones, another 9,000 beds have been made available for mental patients and another 11,500 are being provided.

College of Physicians and Surgeons of South Africa.—The College of Physicians and Surgeons of South Africa was incorporated last July. Until Jan. 17, 1956, it will be possible for doctors on the South African medical register to join as associate founders by payment of a fee, but after that date all admissions will be by examination. The electorate of founders and associate founders will then proceed to elect the first college council. The function of the college is to promote the study and practice of medicine and allied sciences and to maintain standards of professional conduct. Examinations will be conducted, and research and postgraduate teaching are to be promoted.

Queen Visits Veterinary School.—The Queen and the Duke, on their first visit to Cambridge since her accession, saw an electrocardiograph in operation at the new school of veterinary medicine, which she opened. The patient, a 14-year-old horse, stood quietly while the electrodes strapped to his legs were connected with the electrocardiograph. The Queen and the Duke watched the graph of the horse's heartbeats being recorded and were told that the recordings showed that his heart was normal. In opening the school, the Queen said: "We look to veterinary medicine to play an important role in the solution of the urgent problems that confront us."

After-Care of Patients.—General practitioners sometimes complain to the medical press that they are not kept informed of the progress of patients referred to hospitals. This criticism could not be leveled at the hospital that wrote the following letter to a general practitioner: "Dear Doctor, Mr. ——, of ————, aged 52, who was admitted to this hospital on Sept. 15, 1955, died on Oct. 30, 1955. We are sending this notification so that you may be able to arrange for the appropriate after-care."

Chemical Microbiology.—A new chair of chemical microbiology has been established at Oxford. A brewing firm has agreed to contribute $1,870 a year for 21 years in its support. Dr. D. D. Woods has been appointed as the first holder of the new chair, known as the Iveagh Chair of Chemical Microbiology. Dr. Woods is best known for his work on the mode of action of the sulfonamides, which act competitively with para-aminobenzoic acid.

GERMANY

Health Insurance.—On Sept. 30 the Deutsche Ärztetag (convention of German physicians) took a stand on the reform of the health insurance planned by the Adenauer administration. The resolution demanded among other things that only those should be covered by the health insurance who are unable to protect themselves against the risks of an illness. Furthermore, the feeling of personal responsibility should be strengthened in those who are insured; they should be obliged to contribute to the costs of medical treatment, to the extent to which their economic status makes this possible. The size of the family of the insured should be taken into consideration. Furthermore, it should be possible for the insured to select that form of insurance that seems most suitable for them. Prophylactic examinations and medical consultations while the insured are in good health should be included in the obligations of the insurance. The insured should be allowed to select the physician in whom he has confidence. Everything the physician learns about his patient in the course of treatment is under the seal of professional secrecy; this should apply to health insurance as well as to private practice. Adequate compensation should be received for medical services so that the physician can give his patients all the care they require and keep abreast of the progress in medicine. The health insurance should be restricted to its essential task, the protection against the financial risk involved in an illness. It should not be overburdened with functions that are the field of the governmental welfare agencies.

ITALY

Poliomyelitis in Italy.—At a meeting of the Filippo Pacini Medical Academy of Pistoia, Prof. Gaetano Salvioli said that, on the basis of more than 5,000 cases of poliomyelitis treated at the Antipoliomyelitis Center of Bologna, it was possible to determine the course of the disease in Italy. He reported the results of a comparative study of 500 cases of acute poliomyelitis in patients treated at the center during the epidemic of 1939 and of 1,000 acute cases in patients treated in 1953. On both occasions most of the cases occurred in the spring, and the rural and urban populations were equally affected. Infants were most frequently affected, but on both occasions the cases that occurred in older persons were severer in their clinical aspect, course, and mortality. Susceptibility to poliomyelitis begins after the first months of life. This may be due to the wide diffusion of the virus, the action of which in most persons is not harmful. This should be considered before a vaccination program is undertaken. The problem of vaccination varies greatly from one region to another in view of the diffusion of the virus, its different types, and the varying ways in which it enters the body. An evaluation of the Salk vaccine, with regard to the length of the protection it confers, has not as yet been made. Should it confer a protection that disappears in a short time, the likelihood of the disease attacking older persons, in whom it runs a severer course, would be increased.

Professor Mazzitelli said that vaccinations may have to be restricted to persons who are predisposed to poliomyelitis because of a deficiency of antibodies. In a series of 175 patients with poliomyelitis the speaker observed that the persons most frequently affected were between 3 months and 7 years of age.

In 92.5% the patient was the last-born child of a family that had several children in the susceptible age group. The difference in the age incidence of poliomyelitis in Italy from that of such countries as Sweden and the United States may be due to the prevalence here of a different strain of the virus.

NEW ZEALAND

Primary Aldosteronism.—Sayers and his co-workers (*Lancet* **2:** 63, 1955) reported the case of a 37-year-old woman who had been in good health until halfway through her third pregnancy. At that time she began to suffer from recurrent attacks of weakness affecting only the skeletal musculature, although there was no weakness in the muscles supplied by her cranial nerves. Her legs were often affected alone and were always weaker than her arms. Her serum potassium level on admission to the hospital was 2.41 mEq. per liter. When treatment with 8 gm. of potassium chloride was begun, her condition changed dramatically. There was a return to normal of her serum potassium level as well as a complete recovery of her muscle tone, power, and coordination. When potassium chloride was withheld, she soon relapsed to her previous state of weakness, lethargy, and depression. Studies of renal function showed only slight damage. When extracts of this patient's urine were assayed, they were found to have an increased aldosterone-like activity, as compared with those of normal persons.

Effects of Halocortisols and Prednisone on Cutaneous Homotransplants.—Woodruff and Llaurado (*Proc. Univ. Otago M. School* **33:**31, 1955) reported the results obtained on the survival of cutaneous homotransplants in rabbits given 1 mg. per kilogram of body weight of fluorocortisol and chlorocortisol acetates and prednisone daily. While the survival time of the grafts, determined by serial biopsy, was seven days in the control animals, in the rabbits treated with any of the three steroids, it was about two weeks. This modification of the reaction to skin homotransplants is analogous to the response obtained earlier by Professor Medawar of London by administering 10 mg. of cortisone daily, but the effectiveness of the new steroids proved greater considering the smaller doses used. It was also observed that (1) the grafts took longer to become adherent to the host, (2) contraction of the raw area on the host was slower, and (3) the end point of the homograft reaction was less sharp in the treated animals than in the controls. All the recipients lost weight during the experiment, but the treated animals lost significantly more than the controls.

Chemically Induced Granulomas.—Dr. H. C. W. Stringer (*Proc. Univ. Otago M. School* **33:**28, 1955) reported the results of work done on the induction of cutaneous granulomas designed to represent a disease form free from bacterial life and special immunity and to be sufficiently like naturally occurring granulomas that they could be used to test therapeutic agents. The granulomas were induced by injecting 0.01 ml. of either 10% phthioic acid in ethyl alcohol or sterile cod liver oil in the skin of a mouse and were viewed through windows of a modified Algire pattern. Inflammatory changes about the injected areas developed into granulomas in 8 to 10 days, and the lesions persisted for as long as five weeks. The gross appearance was that of a thickened plaque of tissue surrounded by active blood vessels. Microscopically the injected area at first showed swelling and invasion by polymorphonuclear and mononuclear phagocytes. Later the exudate contained densely aggregated mononuclear cells with a foamy cytoplasm.

Hypothermia in Sheep.—Borrie and Woodruff (*Proc. Univ. Otago M. School* **33:**33, 1955) described a technique for inducing hypothermia in sheep. After starvation for two days and premedication with morphine, atropine, and brevidil, the animal is immersed, except for its head, in a bath at 4 to 6 C. A thermopile is inserted in the rectum. Shivering is controlled by administering ether through an intratracheal tube connected to a pump used for artificial respiration or by further injections of brevidil. When the rectal temperature reaches 30 C (86 F), the animal is removed from the bath and roughly dried. There have been no deaths attributable to hypothermia since this technique was adopted. Fourteen operations have been performed successfully, including simple occlusion of the abdominal aorta and of the thoracic aorta and insertion of a polyethylene prosthesis into the thoracic aorta. The thoracic aorta has been occluded for up to 38 minutes and the abdominal aorta for up to 65 minutes without paraplegia resulting. After the operation, the animal is rewarmed in a bath at 45 C. When the rectal temperature reaches its normal level of 38 to 39 C (100 to 102F), the animal is carefully dried and provided with a warm jacket. It is able to stand almost immediately and is then returned to its pen.

SWITZERLAND

Prolonged Treatment with Cortisone.—Dr. F. Layani of Paris, in an address before the Geneva League Against Rheumatism in October, said that in the six years since the introduction of cortisone we have learned that (1) it does not act on the causal factor or factors in polyarthritis; (2) the disease is not characterized by clinical or biological signs of hypophysial-adrenal insufficiency; and (3) hormone therapy, to be effective, must be prolonged. Statistics indicate that only about 50% of patients are benefited. About 67% of those who are benefited, however, gradually become somewhat resistant to the hormone, and doses must be increased. In patients in whom the use of the drug is prolonged, the incidence of accidents varies from 20 to 100%. They are three times more common with doses of 75 mg. and over than with smaller doses. They are also more frequent in women and children than in men. Psychic disturbances are common. Some other disadvantages of long-term corticotherapy are: the need to adjust the dose continually; variability of the maintenance dose; necessity for constant medical supervision; and necessity for preliminary examinations to exclude the possibilities of tuberculosis, viral or bacterial infection, diabetes mellitus, peptic ulcer, and hypertension. Long-term therapy is justified on the basis of the amount of functional recuperation it can impart. Pure, nonacetylated hydrocortisone is a valuable agent. In tablets of 10 mg. each, it is as easily absorbed as cortisone. Its effects are felt after a few hours. Its proper dosage is two-thirds that of cortisone. For maintenance, between 30 and 60 mg. is given daily, divided into three or four doses. Patients with polyarthritis can be benefited by this drug after they no longer respond to cortisone. It is better tolerated than cortisone, but, like cortisone, it loses its effectiveness after prolonged administration. More patients are benefited by hydrocortisone than by cortisone.

New enthusiasm has been engendered by the use of prednisone, but this has been dampened by the appearance of severe reactions in some patients. Dr. Layani used it in the treatment of 52 patients, of whom 40 had polyarthritis. Most of these patients have been followed for more than six months. They experienced a prompt amelioration of symptoms, and, after two to four weeks, inflammatory signs practically disappeared. Periarticular infiltration and effusion into the joint were relieved more slowly. The long-term results are variable. New bouts of rheumatism may occur while the patient is under treatment. In general, however, the results after six months of treatment are favorable. They surpass those obtained from other hormones. There is a gain in functional capacity that allows a return to satisfactory social activity. In Dr. Layani's series two cases of diabetes occurred (one with acidosis). Although prednisone, like cortisone and corticotropin, may be attended by untoward effects, it still has the advantages of being more active and easier to manage and of not causing water retenion.

CORRESPONDENCE

EMPHYSEMA

To the Editor:—We would like to commend the timeliness of the editorial "Emphysema and Its Relationship to Dust Exposure" in the Aug. 27, 1955, issue of THE JOURNAL, page 1526. It is certainly true that "the whole subject of pulmonary emphysema, whether or not related to the dust diseases, needs further definitive study." We believe the problem of emphysema is of considerable urgency since the incidence of this condition appears to be increasing in industry, where the issues involved are of great practical importance. The pragmatic and academic questions involved have held our attention for some time. In fact we are in the midst of the preparation of a comprehensive review on this subject. In this editorial ample stress was put on lack of understanding of emphysema and its relationship to dust exposure. Yet it is concluded that "In the present state of our knowledge, it seems likely that focal emphysema per se is not a serious cause of impaired lung function." It is even suggested that diffuse obstructive emphysema due to other than industrial causes is responsible for pulmonary disability found in coal miners showing simple pneumonoconiosis by chest roentgenogram. It should be noted that this trend of thought was applied recently also to simple silicosis by Wright (Symposium on Occupational Diseases of Lungs: Functional Abnormalities of Industrial Pulmonary Fibrosis, *A. M. A. Arch. Indust. Health* **11:**196 [March] 1955), who stated: "When clinical or physiologic evidence of impairment consistent with diffuse obstructive emphysema is observed in a person with simple discrete nodular silicosis, one must suspect that the emphysema is a chance concomitant disease and would have occurred even though the silicosis were absent." These points of view with which we take issue have their theoretical as well as practical aspects.

We believe the error in logic in extrapolating from the coal miner's emphysema described by Gough to emphysema due to dust exposure should be pointed out. The focal emphysema occurring in relation to anthracosis is such a distinctive phenomenon that it may be seriously questioned whether it bears any relation to other forms of emphysema of industrial origin, for instance, such as is found to occur in relation to silicosis. In its initial stages coal miners emphysema is really a cystic bronchiolectasia and frequently the distention of the respiratory bronchioles leads to compensatory or mechanical atelectasia of adjacent alveoli. In a strict sense a true emphysema arises only when distention of the respiratory bronchioles secondarily encroaches on the alveoli and causes these to dilate or coalesce. In obstructive emphysema, whether it be of occupational or nonindustrial origin, the primary anatomic manifestation of the emphysema affects the alveoli while the respiratory bronchioles remain either unchanged or may be narrowed. It should also be pointed out that varying degrees of vesicular emphysema, "obstructive" and otherwise, occur almost universally in long-term employees in industries where there are substantial exposures to free crystalline silica dust. The suggestion that disabling emphysema occurring in industrial workers is a mere concomitant disease, though there may have been an adequate history of occupational exposure and there may already be radiological evidence of pneumonoconiosis, cannot be passed unchallenged. Besides the growing evidence of the association between the emphysema and exposure to industrial environments in which siliceous and other dusts or fumes may be generated, there is now conclusive experimental evidence available that diffuse vesicular atrophic emphysema, diffuse vesicular hypertrophic emphysema, obstructive emphysema, compensatory emphysema, and focal emphysema may all be provoked by the inhalation of specific types of dust and fumes. Vesicular atrophic emphysema has been best produced by means of exposure to beryllium oxide; vesicular hypertrophic emphysema has resulted from the inhalation of certain types of submicron amorphous silica dust, while exposure to other varieties of particulate amorphous silica has led to obstructive emphysema with associated bronchial polyposis and stenosis. Compensatory emphysema is a common accompaniment of experimentally induced silicosis. Focal emphysema (dilated respiratory bronchioles) has been most successfully induced by prolonged inhalation of an aerosol derived from a blend of rare earth fluorides. Interestingly enough, and in complete refutation of the concept of Gough, the focal emphysema appeared before there was any marked focal accumulation of the rare earth fluoride particles in the walls of the respiratory bronchioles, and the suggestion has been advanced by one of us (G. W. H. S.) that the mechanism of origin of the emphysema may be neurogenic in the sense of a dissociation of the parasympathetic and orthosympathetic tone of the respiratory bronchioles (The Biological Action of Rare Earths: II. The Experimental Pulmonary Histopathology Produced by a Blend Containing a Relatively High Fluoride Content, *A. M. A. Arch Indust. Health* **12:**306 [Sept.] 1955). The inhaled nocuous agent may also act as a direct toxic substance injuring the alveolar walls and impairing their function. Of topical interest in this connection is the recent report by Bonnell (Emphysema and Proteinuria in Men Casting Copper-Cadmium Alloys, *Brit. J. Indust. Med.* **12:**181 [July] 1955) showing that emphysema may develop in relation to the inhalation of fumes generated in the process of casting copper-cadmium alloys.

A further theoretical issue involves the fundamental question of whether airway obstruction is invariably the cause or effect of emphysema. The prevailing concept of the primarily obstructive nature of emphysema is difficult to reconcile with the findings in focal emphysema where the essential lesion is dilatation of the respiratory bronchioles. The conclusion is therefore drawn that focal emphysema cannot lead to pulmonary disability and when the latter is present it must be explained by the assumption of additional obstructive emphysema of undetermined origin. Obviously the prevailing concept of obstructive emphysema leads to theories that are, to say the least, far-fetched. In recent publications, two of us (E. M. and I. R.) have argued in favor of the concept that airway obstruction may be a sequel and complication that aggravates and precipitates pulmonary disability but is not necessarily considered always the primary cause of emphysema (Clinical Observations and Interpretations of Abnormal Airspaces in the Lungs: New Concept of Their Origin, *J. A. M. A.* **153:**700 [Oct. 24] 1953). There is much physiological, pathological, and clinical evidence in favor of the functional rather than structural nature of airway obstruction in emphysema. Of recent physiological studies those of Dayman (Mechanics of Airflow in Health and in Emphysema, *J. Clin. Invest.* **30:**1175 [Nov.] 1951) and of pathological studies those of Kuschner (Emphysema and Exposure to Respiratory Tract Irritants: Pathological Aspects, read before the 14th Annual Congress on Industrial Health, Louisville, Ky., Feb. 24-25, 1954) deserve particular mention. As to the clinical evidence, the frequent favorable effect of bronchodilator drugs speaks against the invariably irreversible structural nature of airway obstruction in many varieties of emphysema. In our concept the advent of complicating functional airway obstruction in cases of focal emphysema is an expected natural development. It occurs by virtue of the same reasons that lead to secondary obstructive phenomena in emphysema regardless of origin. We believe the crux of the problem to be the factors in

the genesis of emphysema itself, not the airway obstruction. Focal emphysema is a unique and puzzling phenomenon in more senses than one. 1. As a pathological change it is unique since it develops in coal miners, graphite workers, and welders in relation to heaping up of dust in the terminal lung structures rather than because of fibrosis of these but is not quantitatively related to the amount of accumulated dust particles and can under experimental conditions occur before there is any focal deposition of dust. 2. It stands as incontestible evidence of emphysematous changes associated with dilatation rather than narrowing of the air passages. 3. Although the emphysematous changes in the lungs may reach a relatively marked degree, they need not be associated with the clinical picture of diffuse pulmonary emphysema. 4. When pulmonary disability of an emphysematous character develops in cases of focal emphysema the clinical and pathological features are indistinguishable from those of any other form of disabling diffuse pulmonary emphysema. That focal emphysema is a pulmonary condition of industrial origin has been established beyond doubt. As diffuse hypertrophic vesicular emphysema also may occur in association with focal emphysema, is it reasonable to dissociate focal emphysema from the other causes of diffuse pulmonary emphysema and assume that the inhaled dust that causes it cannot at the same time cause other varieties of emphysema? This is of particular importance from the standpoint of the medicolegal evaluation of the cases of disabling focal emphysema in clinical practice. Here we must be guided by reasonable assumptions within the limits of our knowledge. This is the practical issue.

We are inclined to take a dim view of the trend to make speculation the basis of decisions in practice. We believe it is mere speculation to assume that simple pneumonoconiosis cannot be associated with dust-provoked disabling emphysema. The pneumonoconiotic reaction does not cause the emphysema, but the inhaled dust does. There is therefore no necessary correlation between the degree of pneumonoconiosis and the amount or nature of the emphysema. In our experience we encounter many cases of industrial diseases in the lungs in which clinically and physiologically disabling emphysema does not correlate with the x-ray features of pneumonoconiosis. We believe that at the present state of our knowledge when disabling emphysema is present in cases with adequate history of dust exposure, it is more reasonable to assume causal relationship between the inhalation of dust and the presence of the emphysema than to speculate on possible presence of additional emphysema not of industrial origin merely because signs of pneumonoconiotic reaction are as yet in abeyance.

As we understand it, the crux of the emphysema problem may even be in the individually variable "reserve capacity" of the lungs. In many industrial workers disabling emphysema does not develop until there is well-established associated pneumonoconiosis. In some workers emphysema may develop on excessive dust exposure without accompanying signs of fibrosis. Between these two extremes there is a very wide and fluent range of variations of emphysema in relation to the type and degree of pneumonoconiosis. These discrepancies are, we believe, at least partly explained by the individually variable "reserve capacity" of the lungs and contributing to the factors that may limit such pulmonary reserve is the concept of multifocal "lung defects." As recently suggested by two of us (I. R. and E. M.) "lung defects" remaining from the period of postnatal development of the lungs may account for many of the more striking individual differences in pulmonary reserve as well as the development of emphysema of differing severity in industrial workers exposed to comparable environmental conditions (Emphysema and the Senile Lung, *J. Am. Geriatrics Soc.* **2**:581 [Sept.] 1954).

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POLIOMYELITIS VACCINE

To the Editor:—During the week of Nov. 14, 1955, at meetings of the American Public Health Association in Kansas City, the United States Public Health Service released two reports on poliomyelitis. One report on Nov. 15 presented by Dr. Langmuir's group from the Poliomyelitis Surveillance Committee stressed the great effectiveness of one inoculation of the Salk vaccine used in 1955, namely, a 50 to 80% reduction in paralytic poliomyelitis. The other report on Nov. 17, presented by Dr. Scheele, stressed the safety of the current Salk vaccine. The widespread national publicity that followed these reports naturally led the public and medical profession at large to believe that we now had a safe and highly effective vaccine. However, what was not made sufficiently clear in the reports and the press stories that covered the country was that the first report, stressing excellent effectiveness, referred to an earlier model of a Salk vaccine and that the second report, stressing current safety, referred to a later model. The effectiveness report on the earlier model was based on results achieved in children, the bulk of whom received vaccines that were manufactured prior to the development of the postinoculation poliomyelitis cases first reported on April 27. Such vaccines were admittedly the product of a process in which there were "fundamental weaknesses in the safety testing procedures" (Scheele, Aug. 25), which did not have the benefit of the more sensitive cortisone-treated monkey tests (formally required on Sept. 10) and which did not have the advantage of crucial filtration procedures that followed the recognition of "the absolute need for removal of particles within which virus may be protected from inactivation by formaldehyde." (Scheele, Nov. 17)

There is substantial evidence (*Bulletin of the American Association of Public Health Physicians*, November, 1955) indicating that manufacturers' vaccine, other than Cutter's, had varying amounts of live virus in it and that what is being measured for effectiveness is not Salk's killed virus vaccine but a live virus vaccine labeled Salk—obviously powerful but also more dangerous. At any rate, it should be evident that the Salk vaccine, for which great effectiveness is claimed on the basis of one inoculation, is a product that is no longer on the market nor in the hands of physicians (we hope) and that was the product of an inadequate manufacturing process and inadequate and relatively less sensitive safety tests. The report on Nov. 17, dealing with the current Salk vaccine's safety, is the interim report of the Public Health Service Technical Committee on Poliomyelitis Vaccine as published in THE JOURNAL, Dec. 10, 1955. The publication of this report is intended to guide and to keep physicians informed of developments in the Salk vaccine program. The report itself has one striking peculiarity. Though it deals with dated decisions made at specific meetings held since May 26, not one single date is listed in the document. Not even is the date of the issuance of the Interim Report given. It is as if we are dealing with a timeless document that purports to give both active and retroactive reassurance.

Though the intention of this omission of dates is only knowable to the committee, the confusion leading from this omission is knowable to the reader. I will attempt to indicate the extent to which the report has been informative as to the nature of a safer Salk vaccine and, in the practical order, the extent to which this report adds to the current confusion. The summary highlights in the clarification of a safer Salk vaccine are as follows: (1) "the absolute need for . . . suitably spaced filtration procedures" (this provision made its first appearance in the minimal requirements as amended Nov. 11, 1955) and (2) "a safety-test program . . . strengthened by improved sampling procedures . . . and by increasing the sensitivity of the monkey safety tests" (the test utilizing the cortisone-treated monkey made its first appearance in the minimum requirements as amended on Sept. 10, and as reamended on Nov. 11).

However, is this the vaccine that is in the hands of physicians and health departments? The Interim Report itself and the statement of Dr. Scheele, reported in Washington News in THE JOURNAL, Dec. 3, leads us to believe that it is. In the latter news story, it is stated that "production of the Salk poliomyelitis vaccine, which has been lagging . . . will start picking up sometime in December and probably will reach a normal rate by February. Reason for the lag . . . is the major changes

made last May in vaccine production and testing requirements and the continuing refinements since that date . . . [the] modifications were incorporated formally into minimum standards for producing and testing the vaccine on Nov. 11. . . ."

However, it should be clear that the new requirements of last May subsequently resulted in steady production throughout the summer and did not cause the delay in the late fall production referred to above. It should also be remembered, as confirmatory, that in May it was recognized that the new requirements would only halt vaccine production temporarily. Therefore, the delay in production seems to be associated with the minimum requirements amended Nov. 11. In an attempt to confirm this and to discover whether the vaccine in my possession (vaccine with an expiration date of April 6 and 7) conformed to the Nov. 11 minimum requirements for safe production, inquiry was made of the manufacturer, a manufacturer who incidentally happens to be at present the leading producer of the Salk vaccine. The answer was disquieting. Not only did the vaccine in my possession not conform to the Nov. 11 requirements but the more than one million cubic centimeters of vaccine issued by the same manufacturer the week of Dec. 12 also did not conform to the Nov. 11 requirements, insofar as it excluded a crucial filtration step required during the inactivation process. Furthermore, the manufacturer's representative stated that no such vaccine can be expected from them, and presumably other companies, until the end of January, though in the meantime they would continue to release vaccine already in process not conforming to these requirements.

The Salk vaccine, then, which we were encouraged to believe is both highly effective and safe on the basis of recent reports, turns out to be, when highly effective, a vaccine that is no longer on the market and, when safe, a vaccine that has yet to make its appearance and clinically prove its effectiveness. Yet, in the face of this paradox, the public is being urged from all directions, except that of the practicing physician, to get their inoculations immediately. This, in spite of the fact that there is a shortage of vaccine and that the vaccine available is inferior if not obsolete. To complete the picture, other things should be said. All physicians hope and pray that we now have a safe and effective vaccine. This hope, however, should not rob us of our objective and critical faculties. When we have a safe and effective vaccine, we want to know it and not base it on slender, infirm, and contradictory criteria.

Categorically, the following remarks can be said, and I again refer the reader for further amplification to the *Bulletin of the American Association of Public Health Physicians*: 1. The epidemiological techniques of the Poliomyelitis Surveillance Unit for the determination of clinical safety of the vaccine have proved and remain inadequate. This is highlighted in part by the United States PHS in their finding of live virus in a seventh lot of Cutter vaccine, which previously was exonerated on epidemiological grounds. 2. The reporting of poliomyelitis cases associated with the vaccine has proved to be incomplete. The fact that Poliomyelitis Surveillance Unit has dropped the reporting of crucial satellite cases is a case in point. 3. The fact that millions of children have been inoculated without overt and obvious harm is not a criterion for the safety of the vaccine. To begin with, even when a readily detectable live virus Salk vaccine was used in Idaho, only 1 out of over 1,600 children came down with poliomyelitis. This means that had the 7 million children, estimated to have received their first shot in the National Foundation for Infantile Paralysis program, been inoculated with a readily detectable live virus Salk vaccine, 6,996,000 would not had come down with poliomyelitis anyway. The careful surveillance that is necessary to assess safety in a vaccine with lesser amounts of live virus is obvious.

The Idaho data simply confirms the fact that poliomyelitis is a low-incidence disease and that there is a high degree of acquired immunity and many natural factors preventing the occurrence of the disease (as contrasted to an "infection") in the nation at large. In Salk vaccines with lesser amounts of live virus, the crux of the danger lies in the production of carrier states and the development of satellite cases, which the United States PHS has not been surveying since the middle of the summer and which were incompletely surveyed prior to this period. 4. Everyone should recognize that 1955 was a low poliomyelitis year independently of the use of the Salk vaccine, which was only given to 9 million children. The slight contribution that an unsafe Salk vaccine may have made to the reduction of paralytic poliomyelitis in 1955 is counterbalanced by the known contribution it made to the increase in paralytic poliomyelitis in 1955. 5. Physicians should recognize one peculiar aspect of the experts' recent decision to stick to a three-shot schedule for some for 1956 protection rather than one shot for many. Logic would dictate that, with the shortage of vaccine, it is better to have a 50 to 80% reduction of paralytic poliomyelitis in three times the number of people than to have an additional 20 to 50% protection in one-third the number. Presumably, experts are not convinced of the rough studies proving a high degree of effectiveness after one injection or the transferability of these statistics based on a replaced and suspect vaccine. 6. The medical profession should recall, in the light of the findings pertaining to safety in the Interim Report, that during the summer the promoters of the vaccine continued to urge mass inoculations in spite of recognized ignorance on their part. They were in the dark as to what had gone wrong with the Cutter vaccine, which had passed all established safety tests existing at the time. They also urged mass inoculation despite the fact that one of the two major producers of the vaccine since the field trials of 1954 had begun to find live virus in the vaccine back in May, by using testing procedures more stringent than those required by the government, the reasons for which were unknown to the pharmaceutical house and the government. Neither the public nor the medical profession was informed of these justified uncertainties, nor is it certain that we are yet being adequately informed. 7. Finally, we should recognize that only one side of the ledger is being presented by the promoters of this vaccine. The price that has been paid and the risks that have been taken for the dubious results that have been obtained are not mentioned. The price that we have paid, and are continuing to pay, goes far beyond those known vaccinated children who have come down with poliomyelitis.

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DRUG SAMPLES

To the Editor:—Because of the difficulty in getting an adequate supply of drugs in Korea, any surplus samples that could be made available to Graham Hospital would be greatly appreciated. This is a 150-bed tuberculosis hospital with two Korean doctors, an American superintendent, and an American head nurse. The outpatient clinic sees a variety of diseases, including vitamin deficiencies, nontuberculous chest conditions, Clonorchis sinensis infestation, and diabetes. There is therefore a constant need for all types of drugs. Tuberculosis is perhaps the chief medical problem in Korea, and for that reason a number of private agencies are doing what they can to combat it. We now have roentgenograms on about 2,000 patients with tuberculosis whom we are treating either in the hospital or as outpatients. A new building, a gift from Armed Forces Aid to Korea (U. S. A.) and the United Nations Korea Reconstruction Agency will accommodate 75 more charity patients and is especially designed for sanatorium patients. It has a southern exposure and the building is situated so it overlooks a beautiful range of mountains.The situation regarding tuberculosis in Korea can be compared to that in the United States 50 years ago—a high incidence of tuberculosis with an inadequate control program, much of the work being done by voluntary agencies. There is one large national center for the treatment of tuberculosis on the southern coast of Korea, but it is inadequate for the size of the problem.

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BUSINESS PRACTICE

The American Medical Association and the Sears-Roebuck Foundation cooperatively have prepared a brochure entitled "A Planning Guide for Establishing Medical Practice Units." This publication contains practical suggestions on various phases of planning from selection of a site to arrangement of equipment and is available in the libraries of state and county medical society offices. From time to time parts of the brochure, slightly modified editorially, will be reproduced in the Business Practice section of THE JOURNAL.—ED.

PHYSICAL FACTORS IN BUILDING A MEDICAL UNIT

COLD CLIMATE

Orientation is a surprisingly important consideration when placing a building. The shape of the building and how it is placed in relation to the sun can considerably affect the heating and cooling costs and has an important effect on the state of mind of the occupants. Sun glaring into a window can irritate as well as please. Generally a building with its long axis running east and west and its major windows on the south is the least expensive both to heat and to cool. In the northern and colder regions the building should be almost square with its longer axis not more than one and one-half times its shorter axis (fig. 1).

TEMPERATE CLIMATE

In a temperate region the length of a building should be one and one-half times its width, to obtain optimum climatic results. In any event, the length should not be more than two and one-half times the width. In this region a bit more freedom is allowed, but the long axis should not swing more than 25-30 degrees off the east-west direction. The non-air-conditioned building should be so placed that it can take advantage of the prevailing and local breezes for cooling in summer, providing passage of air through the building. Other buildings, trees, and slopes all affect this placement (fig. 2).

HOT-HUMID

In the hot, humid southeast the building should be oriented only with its major exposure toward the south and the north-south to east-west ratio should be at least 1 to 1.5, with the desirable maximum 1 to 3. It has the least cooling load in summer and a desirable heat gain in winter (fig. 3).

HOT-DRY

The hot, arid southwest demands a nearly square building again, and, in opposition to the temperate region, it should be so placed that the winds are blocked or slowed down. The long dimension should still be on the east-west axis and preferably should be no more than one and one-half times the shorter one (fig. 4).

PARKING SPACE

The increased difficulty in parking demands that a successful establishment, be it a bank, a grocery store, or a medical facility, give some thought to parking provisions for its employees and its patrons or patients. Parking areas become more and more a dominant area in planning. Some estimate should be made of probable number of cars to be accommodated. Space for the maximum number need not be provided at the outset in a surfaced area, but space for expansion of the area is desirable.

Parallel parking requires a space about 8 by 24 ft., diagonal parking requires a space between 20 and 24 ft. from the curb and from 12 to 18 ft. along the curb, while about 20 ft. should be allowed for perpendicular parking, with 10 to 12 ft. along the curb. The overall width of the area with drives will be between 20 ft. for parallel parking with one-way drive and 75 ft. for perpendicular parking with two-way drives. You should allow between 400 sq. ft. per car for parallel parking on one side of the drive and 750 sq. ft. per car for diagonal parking on one side of the drive, which includes the total area for parking and drives combined (fig. 5, 6, and 7).

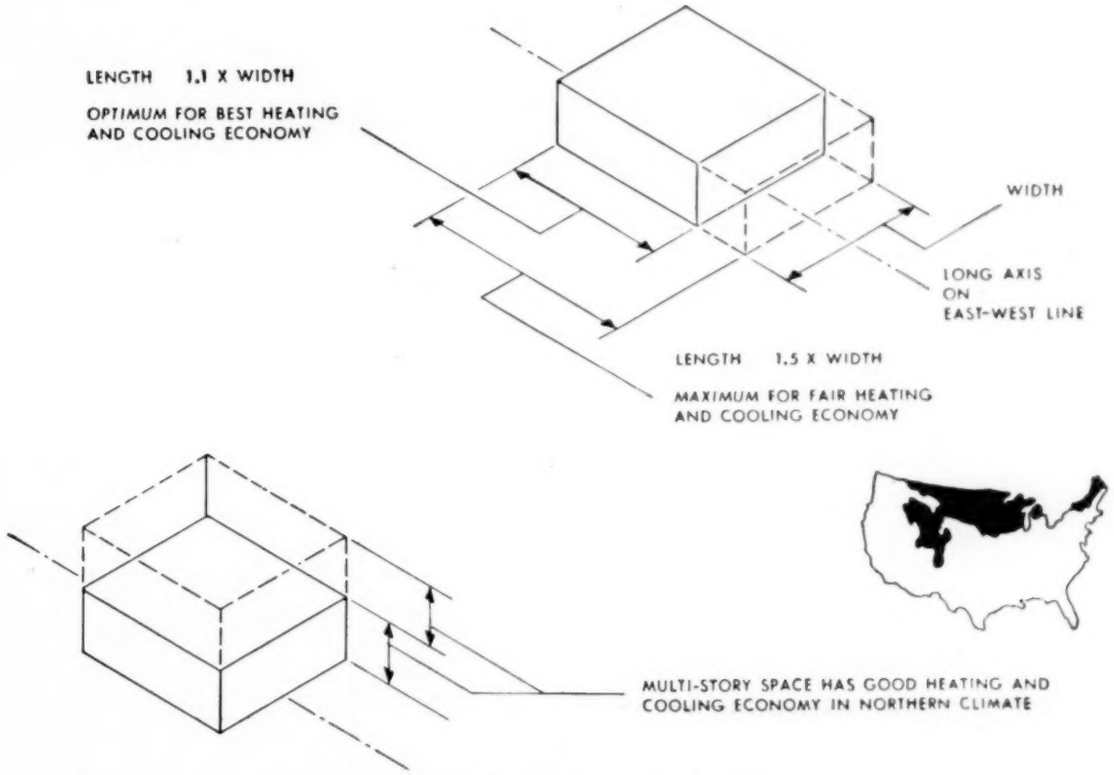
LENGTH 1.1 X WIDTH
OPTIMUM FOR BEST HEATING AND COOLING ECONOMY
WIDTH
LONG AXIS ON EAST-WEST LINE
LENGTH 1.5 X WIDTH
MAXIMUM FOR FAIR HEATING AND COOLING ECONOMY
MULTI-STORY SPACE HAS GOOD HEATING AND COOLING ECONOMY IN NORTHERN CLIMATE

Fig. 1.—Orientation of building in a cold climate.

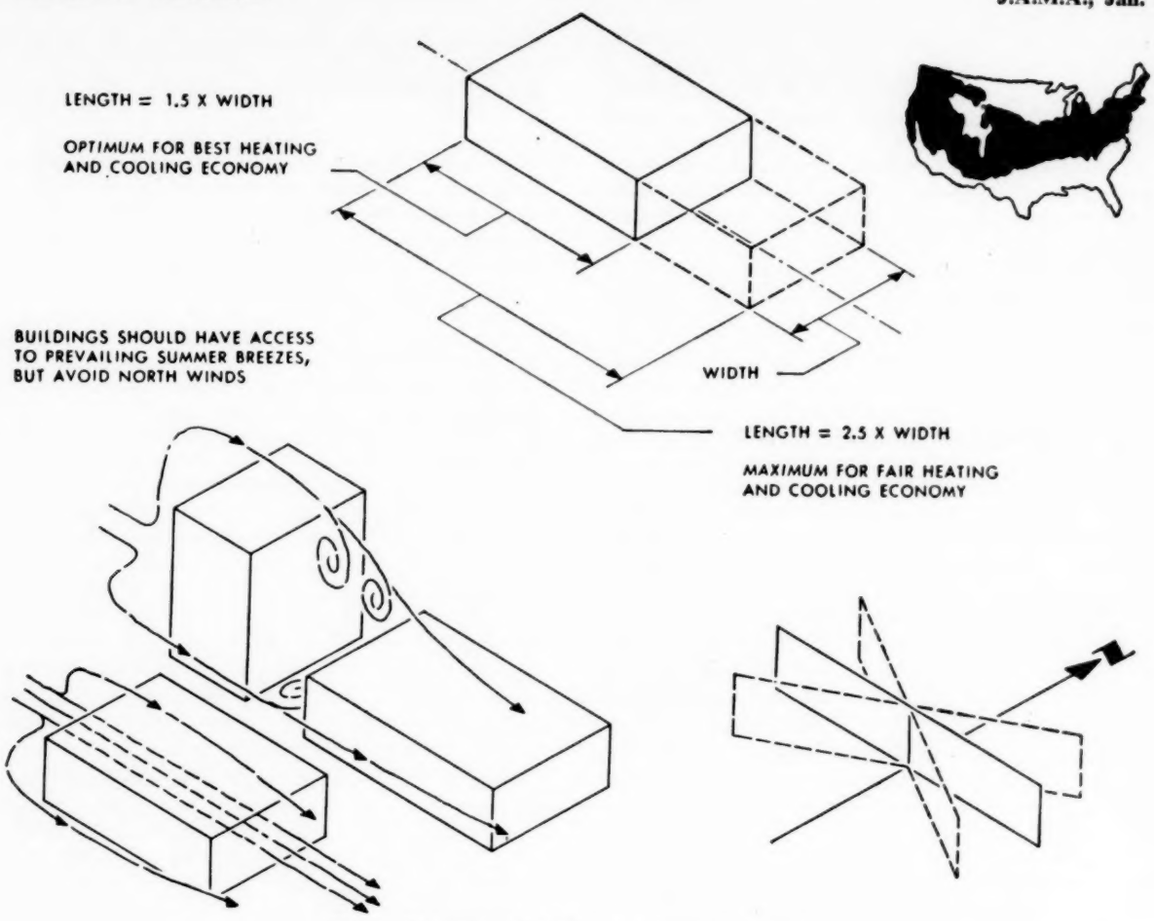
LENGTH = 1.5 X WIDTH
OPTIMUM FOR BEST HEATING AND COOLING ECONOMY
BUILDINGS SHOULD HAVE ACCESS TO PREVAILING SUMMER BREEZES, BUT AVOID NORTH WINDS
WIDTH
LENGTH = 2.5 X WIDTH
MAXIMUM FOR FAIR HEATING AND COOLING ECONOMY

Fig. 2.—Orientation of building in a temperate climate.

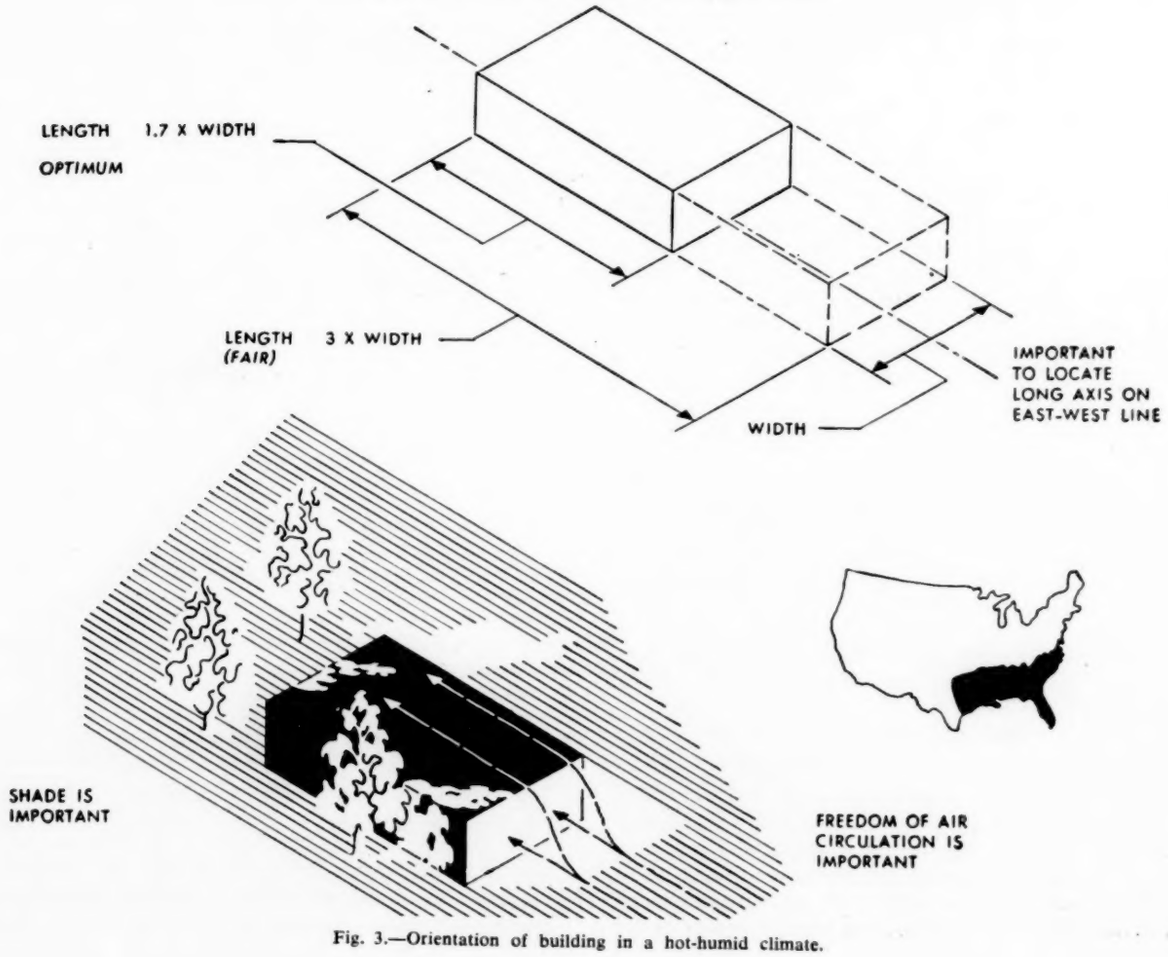

Fig. 3.—Orientation of building in a hot-humid climate.

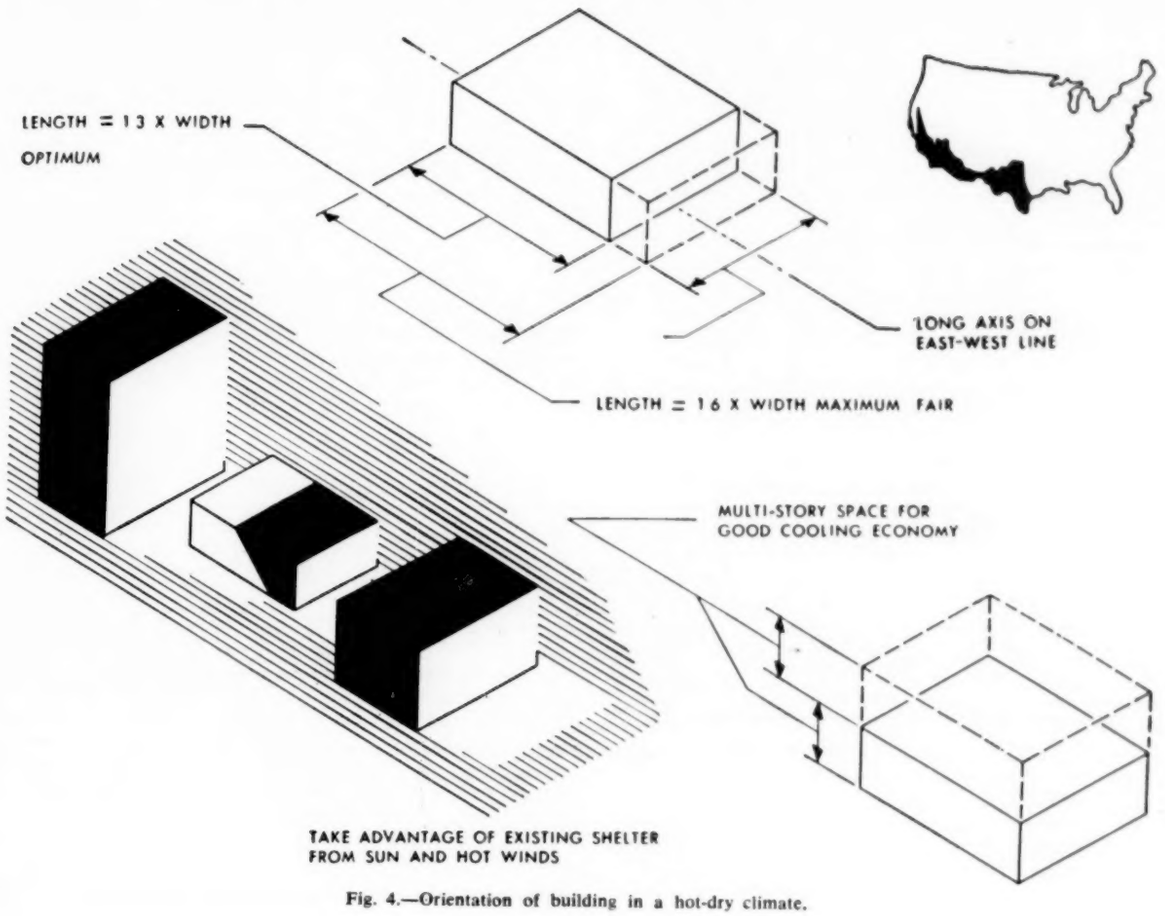
LENGTH = 1 3 X WIDTH
OPTIMUM
LONG AXIS ON
EAST-WEST LINE
LENGTH = 1 6 X WIDTH MAXIMUM FAIR
MULTI-STORY SPACE FOR
GOOD COOLING ECONOMY
TAKE ADVANTAGE OF EXISTING SHELTER
FROM SUN AND HOT WINDS

Fig. 4.—Orientation of building in a hot-dry climate.

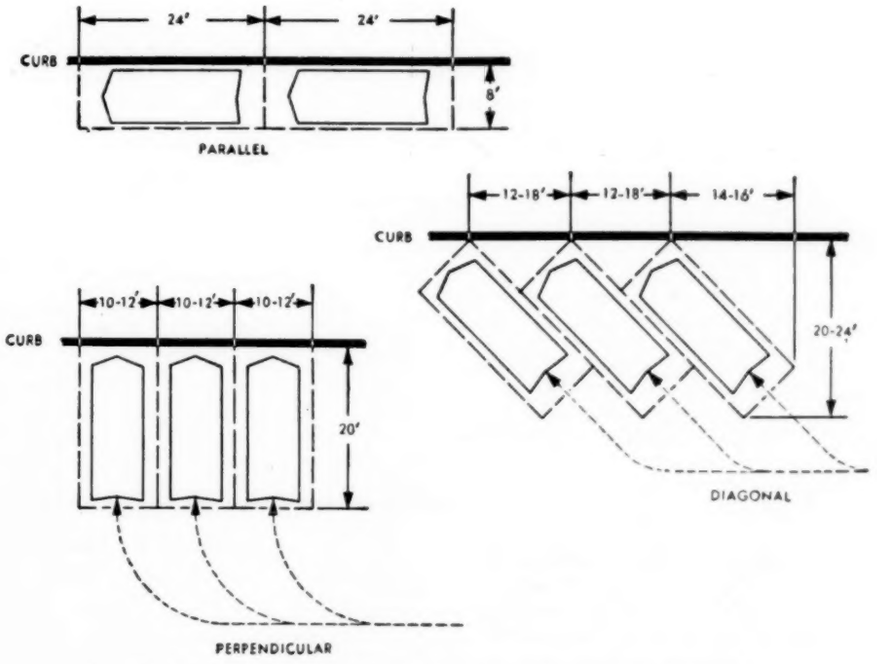

Fig. 5:—Space needed for parallel, diagonal, and perpendicular parking.

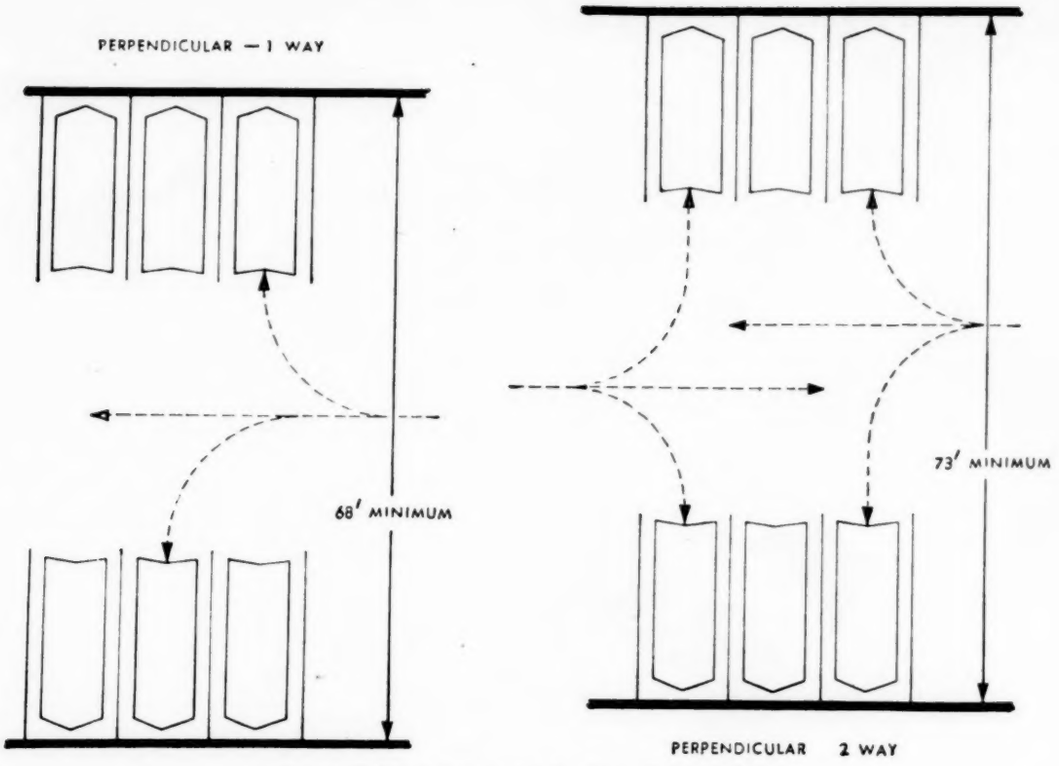

Fig. 6.—Width of area needed for perpendicular parking.

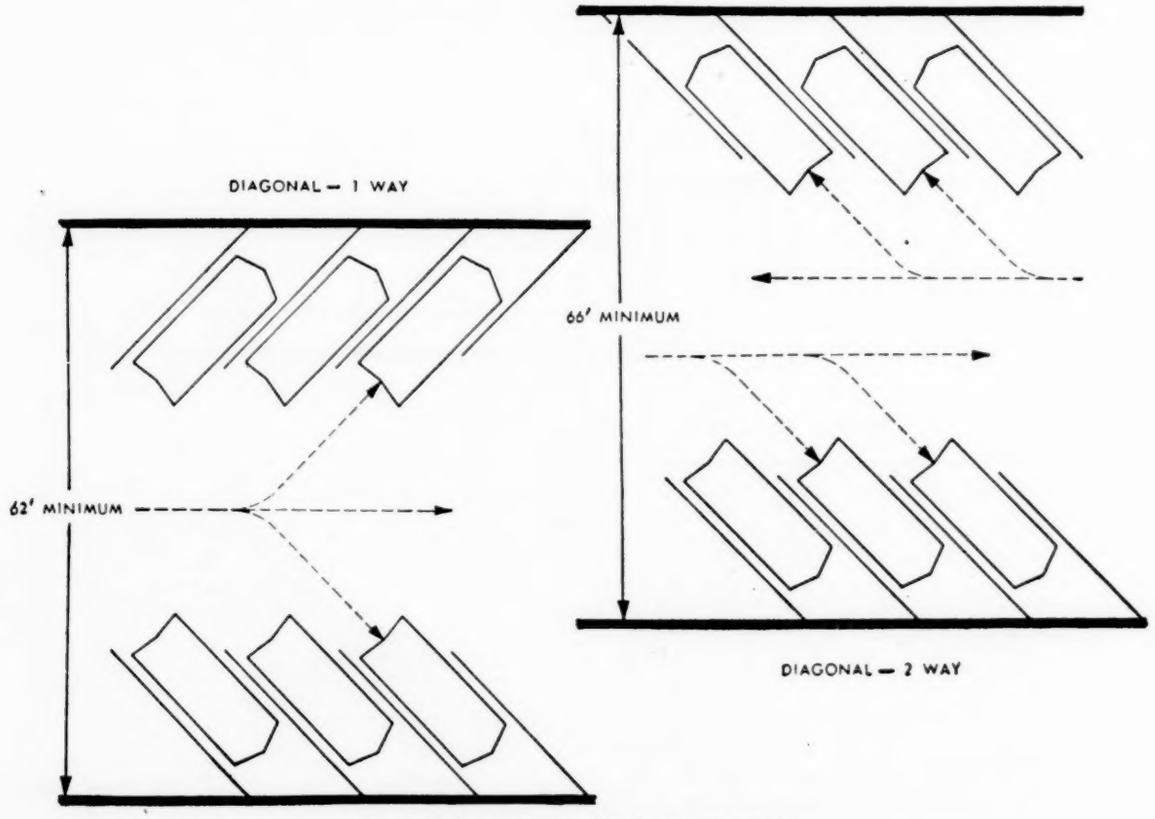

Fig. 7.—Width of area needed for diagonal parking.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Molar Sodium Lactate: Its Effect in Complete Atrioventricular Heart Block and Cardiac Arrest Occurring During Stokes-Adams Seizures and in the Terminal State. S. Bellet, F. Wasserman and J. I. Brody. New England J. Med. **253:**891-900 (Nov. 24) 1955 [Boston].

Molar sodium lactate in doses of from 120 to 150 cc. was given intravenously over 10 to 15 minutes to 46 patients with slow ventricular rates caused by sinus bradycardia, slow nodal rhythm, and partial and complete atrioventricular heart block. The solution was effective in increasing the heart rate in 10 of 12 asymptomatic patients with complete atrioventricular heart block. This effect is apparently the result of an increase in cardiac rhythmicity that involves the higher as well as the lower cardiac pacemakers. The maximum effect was observed at the termination of the lactate infusion or soon thereafter, and the effect as a whole lasted one or two hours after the infusion. Although the effect of molar sodium lactate on the heart rate is quite transient after intravenous administration, results of oral administration of the substance in doses of 90 cc. four times daily for 4 to 10 days in two patients suggested that repeated orally given doses may have a more prolonged action. Because of its effect in increasing cardiac rhythmicity, molar sodium lactate was used for the treatment of patients with cardiac arrest occurring in the course of Stokes-Adams seizures and in terminal cardiac arrest. In three patients in whom Stokes-Adams seizures became manifest, ventricular rhythm was consistently restored after the injection. Molar sodium lactate increased the ventricular rate, decreased the width of QRS complex, and occasionally caused the restoration of a normal atrial rhythm in four patients with hyperpotassemia; the serum potassium level was lowered in these patients, and this decrease was associated with general clinical improvement. In the presence of terminal cardiac arrest in 12 patients, 5 of whom were given molar sodium lactate intravenously and 7, by intracardiac injection, usually two to four minutes after the heart had stopped, the heart rate was restored to about 100 per minute and the configuration of the ventricular complexes was frequently improved. Molar sodium lactate has relatively few untoward effects. The most frequent of these is the development of extrasystoles, which occurred as a transient event in only 4 of the 46 patients, or coupled beats or an increase in extrasystoles already present. These disappear within a short time of cessation of the infusion. Failure to increase the ventricular rate in occasional cases of complete and partial atrioventricular heart block may be caused by insufficient dosage, by irreversible organic damage, and by failure to metabolize the lactate, as was observed in one of the authors' patients.

Regurgitant Esophageal Ulcer. H. W. Schmidt. A. M. A. Arch. Int. Med. **96:**717-723 (Dec.) 1955 [Chicago].

Schmidt discusses regurgitant ulceration of the esophagus on the basis of 170 patients with this lesion seen at the Mayo Clinic over a 10-year period and on the basis of some literature reports. A small percentage of these lesions are congenital, but most occur as complications of the sliding type of esophageal hiatal hernia or of operations upon the gastric cardia. The sliding type of esophageal hiatal hernia is the commonest cause of esophageal ulcers. When patients with this type of hernia are standing, the force of gravity is exerted on the stomach in such a manner that it occupies a normal position. During recumbency or during periods when pressure is applied to the anterior abdominal wall, the cardia and variable amounts of stomach will be pushed into the thorax. Esophagoscopic examination done when this condition is present reveals that the cardia is incompetent, and yellow-tinged gastric juice is seen to regurgitate into the lower part of the esophagus. The most hazardous period, so far as the integrity of the esophagus is concerned, is during sleep. At that time the patient is recumbent and gastric juice regurgitates into the esophagus. Also, during sleep gastric juice is not neutralized by the intake of food. As regards operations on the cardia, the author says that esophagogastrectomy should be avoided, in the case of benign lesions, if it is at all possible, since it completely abolishes the sphincter mechanism of the gastric cardia. Esophagocardiomyotomy seems to be the safest operation to do for cardiospasm, if surgical treatment is necessary, but the results of dilation of the esophagus by means of the Plummer hydrostatic bag have been so excellent for most patients that esophagocardiomyotomy should be reserved for such patients as do not respond to this type of dilation. Dysphagia, retrosternal burning, epigastric pain, pyrosis, vomiting, and hemorrhage are the commonest symptoms of regurgitant ulceration of the esophagus. Of the 170 Mayo Clinic patients, 38 complained of hematemesis and 20 of melena, and 16 said they had had hemorrhages of such severity that blood had to be transfused. Sometimes the bleeding may be unnoticed until the symptoms of rather marked secondary anemia develop. Symptoms of diaphragmatic hernia of the sliding type generally can be eliminated by reduction of weight, if the patient is obese, and by avoiding pressure on the abdomen. If, however, the patient has the classic symptoms of an incompetent cardia and esophagitis, it is best to repair the hernia to restore competency of the cardia and to obviate the risk of the development of regurgitant esophagitis, ulcer, stricture, and short esophagus. It is best not to treat benign lesions of the lower part of the esophagus surgically until all conservative measures have been found ineffective. Medical treatment consists in the use of an ulcer diet and antacids. Patients should be advised to sleep with the head of the bed elevated 6 to 8 in., so that the force of gravity is utilized to keep acid gastric secretions in the stomach. Surgical treatment was resorted to in nine of the Mayo Clinic patients who had rather severe symptoms. Removal of three-fourths or more of the stomach produced good results in seven of these patients, but in the other two the results were poor.

The Relationship of Cirrhosis of the Liver to Hypertension: A Study of 504 Cases of Cirrhosis of the Liver. H. F. Loyke. Am. J. M. Sc. **230:**627-632 (Dec.) 1955 [Philadelphia].

A number of investigators have commented on the absence of hypertension with liver disease. The author investigated hypertension in a consecutive series of patients with cirrhosis of the liver obtained from the records of two hospitals in Cleveland through the years 1943-1954 inclusive. A total of 567 cases was reviewed and of these 504 proved to have a positive diagnosis of cirrhosis. It was found that hypertension is less likely to occur in patients with cirrhosis than in normal individuals. The renal and neurogenic mechanisms capable of elevating the blood pressure remain intact in cirrhosis. This is demonstrated by the fact that hypertension may appear when renal disease develops in a patient with cirrhosis. Furthermore, stress may produce hypertension in cirrhotic patients. Established hypertension was found to be reversed to normal as liver disease advanced to the point of A/G (albumin/globulin) ratio reversal. On the other hand, mildness of hepatic insufficiency cannot account for hypertension in patients with coexisting renal disease, since two of four such patients had such severe hepatic

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The place of publication of the periodicals appears in brackets preceding each abstract.

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lesions as to exhibit reversal of the A/G ratio. This casts doubt on the theory that hypertension is less frequent in cirrhosis because the damaged liver is unable to form the protein substrate on which renin acts. It is possible, however, that the coexisting renal disease was not the cause of the observed hypertension and that in these cases a nonrenal mechanism was operative. The patients in whom the blood pressure fell as the liver failure advanced are the most impressive evidence of the dependence of essential hypertension on adequate hepatic function.

The Double Aspect of Arterial Hypertension. I. Zarday, I. Sebok and Z. Izso. Acta cardiol. **10:**459-475 (No. 5) 1955 (In French) [Brussels, Belgium].

There are two separate aspects of hypertensive disease—one, elevation of pressure in the great arteries (due to peripheral resistance) and the other the capillary phenomena, i. e., ischemia leading to defective irrigation of surrounding tissues. The latter aspect has been grossly underestimated in the literature. For example, cardiac failure in hypertension is most easily explained by constriction of the coronary precapillaries leading to defective myocardial irrigation. Necrosis or autolysis of the arterial wall, caused by the acidosis resulting from the ischemia from precapillary constriction, provides the occasion for the diapedesis seen microscopically in cerebral hemorrhage. In addition to the cardiac and cerebral symptoms of hypertensive disease, renal damage can be explained on the basis of arteriolar constriction. To prove their thesis experimentally, the authors administered caffein in therapeutic doses to some of their hypertensive patients in the cardiological service of their hospital in Budapest, Hungary. They found that it did not increase blood pressure, and they now administer the drug routinely to dilate the coronary arteries and obtain a superior myocardial blood supply. They have observed a decrease in the frequency of cardiac accidents and pronounced improvement in cerebral symptoms, despite the fact that blood pressure was only slightly or not at all decreased during treatment. In cases of hypertensive disease, the physician should concentrate his attention on the capillary and not on the arterial sequelae of peripheral vasoconstriction. The patient should be told that it is not his high arterial pressure but rather the low pressure in his capillaries that lies at the basis of his complaints. This is the essential part of a psychotherapy designed to eliminate anxiety with its consequent increase in adrenal secretion of vasoconstrictive substances. The arteriolar spasm is much easier to treat with modern vascular therapy than increased arterial pressure, which is governed by factors other than peripheral resistance, e. g., the propulsive force of the heart.

Heredity in Gout and Hyperuricemia. M. Hauge and B. Harvald. Acta med. scandinav. **152:**247-257 (No. 4) 1955 (In English) [Stockholm, Sweden].

Recent investigations have provided evidence to the effect that hyperuricemia without manifest clinical attack is a common finding among the relatives of patients with gout. The theory has been advanced that hyperuricemia is the genetic factor in gout. Hauge and Harvald made studies on the relatives of 32 probands with gout. Among 261 close relatives (parents, siblings, children) 16 definite and 2 doubtful cases of gout were observed. In an analogous control series there was only one doubtful and no definite case of gout among 266 immediate relatives. In the two series urinary calculi occurred in 20 and 4 cases, respectively, cholelithiasis in 16 and 18, and diabetes in 5 and 4. Serum urate levels were determined by the Praetorius method in 48 male and 57 female siblings. In the males, the mean value was 6.1 ± 0.2 mg. per 100 cc., in the females 5.4 ± 0.2 mg. per 100 cc. In a control series of the same age distribution the mean value for males was 5.1 ± 0.1 mg. per 100 cc., and for females 4.0 ± 0.1 mg. per 100 cc. Thus, the serum urate values for the siblings significantly exceeded those found in the control series. Comparison within each age group showed an increasing difference with advancing age. The blood groups of the probands and their siblings were investigated with regard to the following systems: ABO, Rhesus, MNS, P, Lewis, Duffy, and Kell. The serum urate values found in the siblings did not differ significantly from a normal distribution. It is, therefore, impossible to draw the line between normal and pathological serum urate values in the siblings. The authors conclude that heredity is an etiological factor in gout. Attacks seem to occur as a rule, but not exclusively, in individuals with high serum urate levels. The latter are determined to a certain extent by hereditary factors, being more often elevated among the relatives of gouty patients than in the general population. In these respects, there is agreement between reported investigations. The interpretation of the results differs, however. The present investigation does not support the current view that hyperuricemia is transmitted as a Mendelian dominant but rather that a cumulative gene action (polymerism) may be operative. It proved impossible to demonstrate any linkage between the predisposition to hyperuricemia and the genes within seven of the blood group systems. Continued studies on the serum urate levels in members of families with hyperuricemia can hardly contribute more towards elucidating the heredity of this condition. More would probably be gained by studying the various steps of uric acid synthesis as well as its excretion by members of affected families. Such an investigation is hardly practicable, mainly because the normal synthesis and excretion of uric acid are not completely understood.

6-Mercaptopurine in Acute Leukemia. F. G. J. Hayhoe. Lancet **2:**903-905 (Oct. 29) 1955 [London, England].

Synthetic analogues of naturally occurring purines and pyrimidines might be expected to act as metabolic antagonists in the early stages of nucleic acid synthesis in the body by entering into the existing enzyme systems in place of the nucleotide precursor they resemble, thus blocking further synthesis. Many such substances have been prepared and clinical trials have been made in various malignant proliferative diseases in the search for an agent that would influence the metabolism of neoplastic cells selectively without causing severe damage to normal cells. The most effective of this group of analogues at present appears to be 6-mercaptopurine. Clinical trials have been made with 6-mercaptopurine, during the last three years, in acute and chronic leukemias, malignant reticuloendothelial disorders, and metastasizing neoplasms of various kinds. The potentialities of 6-mercaptopurine are of particular interest because reports suggest that it may prove more effective than other agents in the treatment of acute monocytic leukemia and acute leukemias in adults. The present report is based on a study of 15 adults with acute leukemia who have been treated with 6-mercaptopurine in the last two years. Seven of the 15 patients experienced remissions, which were partial in 5 patients and complete in 2. The complete remissions occurred in patients with myeloblastic and lymphoblastic leukemia and lasted three months and more than eight months respectively. The partial remissions were obtained in one patient with myeloblastic, one with lymphoblastic, and three with monoblastic leukemia. The author feels that 6-mercaptopurine is at present probably the agent of choice in myeloblastic and monoblastic leukemias of adults.

Relation Between Concentration of Isoniazid in Plasma and in Cerebrospinal Fluid After Oral Administration. H. Malosetti, E. Balea and A. Addiego. An. Fac. med. Montevideo **40:**13-18 (Jan.-Feb.) 1955 (In Spanish) [Montevideo, Uruguay].

The concentration of isoniazid in the plasma and in the cerebrospinal fluid after administration of the drug by mouth to 18 patients who had a lumbar puncture was measured. Kelly and Poet's method for evaluation of isoniazid in biological fluids was used. The drug was given in doses of 3 mg. for every kilogram of body weight, one and one-half hours prior to measurement. The cerebrospinal fluid was almost normal in all cases. The average concentration of isoniazid in the plasma was 5 micromilligrams for every 1 cc. of plasma. In the cerebrospinal fluid it was a little above 4 micromilligrams for every 1 cc. of the fluid. This concentration of isoniazid in the cerebrospinal fluid proved to be far above that which is necessary to inhibit tubercle bacilli in the fluid. The authors conclude that the meninges are easily permeable to isoniazid when the drug is given by mouth and more so in cases with free tuberculous meningitis. Whether or not permeability is hindered in cases of walled-off tuberculous meningitis is not known. If meningeal

permeability in cases of walled-off tuberculous meningitis is satisfactory after oral administration of isoniazid, the intraspinal route should be replaced by the oral route, which is as efficacious and far less dangerous than the intraspinal route. Meningeal reactions that follow intrathecal injection of 5 mg. of isoniazid in patients without tuberculosis and reactions of intolerance to the drug when given intraspinally to patients with tuberculous meningitis are not observed when the drug is given by mouth.

Clinical and Metabolic Effects of Prednisone. J. S. N. Nabarro, J. S. Stewart and G. Walker. Lancet **2**:993-998 (Nov. 12) 1955 [London, England].

Prednisone (metacortandracin) and prednisolone (metacortandrolone) are produced by the dehydrogenation at the 1 position of cortisone and hydrocortisone. Preliminary reports suggested that their glucocorticoid and eosinopenic activities are three to four times those of the parent compounds. Prednisone seems to be a potent glucocorticoid with relatively little sodium-retaining activity and to be valuable when high-dosage steroid therapy is required. This is often the case in patients with leukemia, malignant lymphoma, purpura, or hemolytic anemia. This report deals with the substitution of prednisone for cortisone. The clinical effects of prednisone (30-40 mg. daily) were observed in five cases of lymphatic leukemia, two cases of lymphoma, and one case of the Henoch-Schönlein syndrome. Metabolic studies were made on five of these patients and on one normal and two adrenalectomized subjects. The therapeutic activity of prednisone is about five times that of cortisone. Studies of glucocorticoid activity in adrenalectomized subjects showed increased nitrogen excretion but little effect on blood sugar. Steroid diabetes developed during treatment with prednisone in two patients. Most patients are able to take prednisone (30-40 mg. daily) with a normal sodium intake, because the sodium-retaining activity of prednisone is not increased. Prednisone does suppress the adrenal cortex. The authors emphasize that the substitution of prednisone or prednisolone for cortisone removes only the least serious of the complications. The fact that these new steroids can be given without restriction of salt intake and that there is little risk of edema developing may well encourage prolonged administration in high dosage. Other and more serious complications of steroid therapy are just as easily produced by these new compounds as by cortisone, and when they are being given it is essential to keep the dose as low as possible.

Fatal Suppression of Symptoms During Hormone Therapy. J. A. Page. J. Am. Geriatrics Soc. **3**:890-892 (Nov.) 1955 [Baltimore].

The author presents histories of two patients in whom dissemination of infection and almost complete suppression of the symptoms of fulminating pneumonia occurred during treatment with the hormones cortisone and corticotropin. These cases occurred in a large clinic for rheumatic diseases, in which cortisone and corticotropin are frequently used as an adjunct to physiotherapy and hydrotherapy, as well as for maintenance in refractory cases in domiciliary practice. The two cases differed in two main respects. The first patient had been receiving hormone therapy over a period of months and was at the time of death controlled adequately on therapy with a daily dose of cortisone. The second patient had received a course of corticotropin therapy during a recent admission and was in a nursing home undergoing a further short course for an acute exacerbation. He had had only six injections of 20 mg. of corticotropin gel. Both patients stated that they felt very much better than they had for some time, in spite of the gross pneumonia present in both. There did not appear to be any limitation of physical activity. Cases like these are rather disturbing. It would seem that all patients undergoing hormone therapy of this type require repeated complete clinical examinations, not more than a week apart. The onus for these examinations will of necessity fall on the shoulders of the general practitioner under whose care many of these patients will come. It cannot be stressed too often that these drugs should be used under close supervision, for, in their present form, there are too many side-effects of fatal consequence. These effects are dissemination of bacterial infection, anaphylactic shock, and water retention.

Prednisone and Prednisolone in the Treatment of Rheumatoid Arthritis. F. D. Hart, C. J. M. Clark and J. R. Golding. Lancet **2**:998-1001 (Nov. 12) 1955 [London, England].

The general consensus of opinion is that prednisone (Meticorten) and prednisolone (Meticortelone) are identical as regards antirheumatic effect and that both have a potency some three to five times that of cortisone and of hydrocortisone acetate taken by mouth. In 14 patients with rheumatoid arthritis, cortisone treatment was changed to either or both of these two drugs and back again to cortisone. Assessment of efficacy was based on the patients' own estimation of pain and stiffness, finger swelling measured with jewellers' rings, tenderness over proximal interphalangeal and metacarpophalangeal joints, erythrocyte sedimentation rate, simple function tests, and power of grip. Improvement and deterioration on changing from one drug to the other and on changing back were noted; the patients and nurses were unaware of the transfer to a new form of treatment. The two substances appeared identical in action, and, in doses of one-fourth or one-fifth of the cortisone doses, they proved more effective than cortisone in relieving the symptoms and reducing the signs of rheumatoid arthritis. Of 14 patients 9 preferred either prednisone or prednisolone to cortisone, 5 were indifferent, and none favored cortisone. In each detailed assessment prednisone appeared as good as, or better than, cortisone, and in no respect did cortisone prove superior. Over-all improvement took place in 10 of the 14 patients on transferring from cortisone to prednisone therapy, whereas 8 deteriorated somewhat on returning to cortisone therapy.

SURGERY

Discrepancies Between Subjective and Objective Responses to Mitral Commissurotomy. G. G. Bergy and R. A. Bruce. New England J. Med. **253**:887-891 (Nov. 24) 1955 [Boston].

Questionnaires designed to probe attitudes and facts of the medical record were sent to 52 patients who had undergone mitral commissurotomy in Seattle and who had survived the operation. Thirty-one (60%) of these patients were willing to return for reevaluation at an average of 21 months after operation. In addition to a careful history, review of the work and recreational records, and physical and laboratory examinations, these patients were reevaluated for standard exercise tolerance. Although questionnaires revealed that 29 of the 31 patients considered themselves "better" as a result of the operation, 16 had higher, 6 the same, and 7 lower physical-fitness index scores. Thus, there was a correlation with objective evidence in only 55% of the patients. Of the remaining two patients, one said that he was "the same" but had a lower physical-fitness index postoperatively, whereas the other, who gave no answer and really believed that she was worse, had a higher index. Most patients still needed some form of medical therapy, and half of the patients still needed daytime periods of bed rest. These two facts, in contrast to subjective opinions, correlated with objective findings on physical examination and standard exercise tolerance tests. For some patients the term "better" described a change in attitude toward their disease and disability rather than improvement in cardiorespiratory function. Changes in attitude may be due to the interaction of several factors. The enthusiastic and positive approach by the surgeon is important, especially when it is coupled with the belief by the patient that improvement will ensue. Once surgery has been accomplished, the patient is emboldened to change his way of life. Careful medical supervision, with a close doctor-patient relation before, during, and immediately after operation, brings about subjective as well as objective benefits. The most important effects of surgery were the decreased intensity and frequency of dyspnea and fatigue after effort. These changes were corroborated by the improvement in the work record for 15 patients who were able to work full time without limitations, in contrast to only 3 patients preoperatively. They were further confirmed by the corresponding changes in symptoms in relation to the standard work load of the exercise-tolerance test, together with increased endurance, slower heart rate, higher systolic blood pressures during exercise, and higher physical-fitness-index scores. A few pa-

tients, despite an improvement in attitude, continued to have specific job limitations, required easier jobs, and were physically unable to participate in fairly sedentary recreational activities, because of diminished cardiac reserve. Possibly, these patients had chiefly myocardial insufficiency, which may be manifested by heart failure, in part caused by carditis, or the postcommissurotomy syndrome often associated with rheumatic heart disease. While attitudes toward heart disease and disability are greatly improved after mitral commissurotomy, there is only partial improvement in the findings on clinical examination and in the patient's ability to meet the requirements of daily life. Objective laboratory evaluation in terms of responses to standard exercise shows only moderate improvement, which hardly exceeds that observed in some patients not operated on. Discrepancies apparent in the clinical evaluation of mitral commissurotomy may arise from failure to differentiate subjective attitudes from objective findings, to provide quantitative measurements of functional capacity before and after the operation, and to realize that surgical therapy is only incidental to one facet of rheumatic heart disease. The final appraisal of mitral commissurotomy must await the objective demonstration of significant differences in functional capacity and longevity after operation.

Incidence of Asymptomatic, Active Rheumatic Cardiac Lesions in Patients Submitted to Mitral Commissurotomy and the Effect of Cortisone on These Lesions: Clinical and Histopathologic Study of Sixty Cases. J. R. Gil, H. Rodriguez and J. J. Ibarra. Am. Heart J. **50:**912-920 (Dec.) 1955 [St. Louis].

Of 60 patients submitted to mitral commissurotomy between 1952 and 1953, 14 were treated with cortisone before as well as after the commissurotomy in order to evaluate the incidence of asymptomatic but active cardiac rheumatic lesions; the effects of cortisone on these lesions as well as on the inflammatory reactions secondary to the surgical trauma; and whether or not the postoperative follow-up in the treated patients is more favorable than in the untreated group. During the commissurotomy, a biopsy specimen was taken from the left atrial appendage of all the patients and also from the pericardium in a few of them. The histopathological study of these specimens revealed active endomyocarditis in 36 (60%) who were asymptomatic; signs of being in the process of cicatrization were revealed in 9 (15%) and healed lesions in 15 (25%). Comparison of the presence and degree of active rheumatic lesions in relation to the proportion of patients treated and not treated with cortisone showed that the use of cortisone diminished the presence of such lesions from 67.4% to 35.7%. It increased the frequency of lesions moving toward cicatrization or already healed from 10.9% to 28.6% and from 21.7% to 35.7% respectively. Cortisone can decrease the inflammatory surgical reactions of the pericardium and endomyocardium. Clinical phonocardiographic and electrocardiographic studies showed that the frequency of postoperative pericarditis decreased from 86.3% in the untreated patients to 38.4% in the treated and that the frequency of alterations compatible with a pericarditis decreased from 72.7% to 36.3%. Histopathological studies revealed a decrease of these changes from 50% to 21.4%. It was not possible clearly to establish a better evolution in the postoperative period in those patients treated with cortisone as compared with the controls. However, relapses and postcommissurotomy syndrome were less frequently observed in the first group. The authors' results show that further investigation is needed.

Surgical Emphysema of the Face, Neck, and Upper Thoracic Wall Associated with Fracture of the Facial Skeleton. I. H. Heslop. Brit. J. Plast. Surg. **8:**243-248 (Oct.) 1955 [Edinburgh, Scotland].

The author presents the case of a 30-year-old man, who was found lying semiconscious in the roadway beside a motorcycle that he had been riding. Apart from maxillofacial injuries, the only damage was slight bruising of the right leg and left knee. Inspection of the injured area showed gross swelling of the whole face, particularly the eyelids, so that the eyes were almost closed; marked swelling in the region of the left angle and left body of the mandible; less marked swelling of the neck and upper anterior thoracic wall; right and left circumorbital ecchymosis; left subconjunctival hemorrhage; hemorrhage from the right external auditory meatus; hemorrhage and leakage of cerebrospinal fluid from the nose; and lacerations of the left eyebrow, upper lip, and chin. Marked surgical emphysema was present from the supraorbital ridges above to the line of attachment of the platysma over the upper thoracic wall below and laterally to the posterior border of the mandible, and in the neck posteriorly as far as the sternomastoid region on each side. The patient had blown his nose repeatedly in an effort to clear the obstruction due to blood clot in the nasal passages. The author comments on the occurrence of surgical emphysema of the face and neck, pointing out that, when surgical emphysema of the face in more gross fractures of the facial skeleton is considered, three points present themselves. First, in view of the multiple communications that must exist between the mouth, nose, and paranasal sinuses and the tissue planes, is it not surprising that extensive surgical emphysema of the face and neck is not a more common accompaniment of such fractures? This thought applies particularly in connection with the fracture of the middle third of the facial skeleton, where breaks in the walls of the air sinuses are numerous. Secondly, is the explanation for the apparent rarity of the condition that such patients seldom attempt to clear the nasal air passages of blood and mucus by blowing the nose and are content to breathe through the mouth? Thirdly, is surgical emphysema of the face common, at least in middle third fractures, and does it frequently go undetected because it is not looked for? In the patient under consideration almost all the fracture sites provided pathways for the passage of air under pressure into the tissues, but, as the patient had blown his nose and had not blown with the mouth, the mandibular fracture site could be ruled out as a pathway in this particular case. The probable sites of escape of air are the breaches in the walls of the nose and antra, and as the patient had a frank cerebrospinal rhinorrhea it is surprising that a traumatic cerebral aerocele did not develop. During the operation for reduction and immobilization of the fractures it was interesting to observe that, when an incision was made in the left cheek for placing of a bone pin in the main zygomatic fragment, there was a considerable escape of sanguineous bubbles from the wound. The facial contour had returned to normal 28 days after the operation.

Indications for Skin Grafting in the Primary Treatment of Dupuytren's Contracture. H. Conway and A. F. Fleury. Plast. & Reconstruct. Surg. **16:**264-275 (Oct.) 1955 [Baltimore].

The authors observed 52 male patients with Dupuytren's contracture of whom 41 received surgical treatment. The disease is characterized by thickening of the palmar aponeurosis and marked decrease in the amount of subcutaneous fat. Several different surgical techniques were employed. The simplest of these was subcutaneous fasciotomy. This is readily done through small laterally placed incisions. This procedure was very effective in relieving the contracture in cases without involvement of skin or joints. Dupuytren's contracture is a progressive disease of the palmar fascia and the contracture is very likely to recur following this procedure. All three of the cases in this series that were treated by subcutaneous fasciotomy experienced recurrence of the contracture. The ideal operation is the excision of the entire palmar aponeurosis. The exposure necessary for a true total excision requires rather extensive undermining of palmar flaps, and the precarious circulation of these flaps is well known. Limited excision was employed in most of the cases in this series, attention being directed toward the complete removal of the affected portion of the aponeurosis. Follow-up information was available on 27 patients. Eleven of these were operated for bilateral disease. The results indicate the superiority of limited fasciectomy. Since the total fasciectomy was employed of necessity in the more advanced cases, while limited fasciectomy was most applicable in the earlier stages, this conclusion is not entirely valid. The authors arrive at the following conclusions: 1. The operative procedure in Dupuytren's contracture must be adapted to the individual case. 2. The procedure of choice in the management of the early contracture is the limited excision of the involved palmar fascia through a conservative incision. 3. When contracture of the palmar skin

results in deficient coverage of the extended palm or when skin flaps are of questionable viability, primary skin graft accomplishes the desired result. 4. In a limited number of patients in whom the deformity has progressed to digital ankylosis in flexion and who also have severe fibrosis of palmar skin, it is justifiable to fillet the digit affected most severely and to use the digital flap of soft tissue for coverage of the palm.

Tietze's Syndrome: Results of Treatment with Hydrocortisone. A. Celio and H. Nigst. Schweiz. med. Wchnschr. **85:**1150-1152 (Nov. 19) 1955 (In German) [Basel, Switzerland].

In patients with Tietze's syndrome there generally appears in the course of weeks or months a swelling at the sternal end of the ribs; sometimes the swelling is bilateral. It is accompanied by pain that is localized in the swelling and sometimes radiates toward the chest, arm, or shoulder. The pain is particularly acute in movements of the thorax such as those caused by sneezing, compression, or deep inspiration. The swelling is visible externally. On palpation it gives the impression of being the size of a hazelnut or a prune. It is sensitive to pressure. The skin above it is reddish, but not hot, and it is accompanied neither by edema nor adenopathy. On surgical exposure there are often no visible changes on the bone except that in a few cases there may be a spindle-shaped proliferation at the transition from the cartilage to the bone, bending of the ribs forward, pallor of the bone where it joins the cartilage, or swelling of the soft tissues that cover cartilage and bone. The authors discuss differentiation of Tietze's syndrome from such conditions as tumors, osteitis, periostitis, caries of the ribs, fatigue fractures, osteochondromas, Ewing sarcoma, osteogenic sarcoma, multiple myeloma, rheumatic perichondritis, and cysts of the ribs. The etiology of Tietze's syndrome is unknown. Various treatments have been employed including surgical resection of the rib and of the adjoining cartilage. There may be spontaneous remission of swelling and pain, but without treatment there is also a tendency to relapse. The authors present two cases in which they obtained favorable results with local injection of hydrocortisone. In one of the two patients the symptoms subsided following a single injection, in the other following four injections given within a period of two weeks. Complete regression of the swelling required 10 days in one and three weeks in the other. One year has elapsed since the observation. In view of the unfavorable results obtained with most of the therapeutic methods in Tietze's syndrome, the authors recommend injections of hydrocortisone as a very effective procedure.

The Surgical Management of Tietze's Syndrome. J. T. Nix and M. A. Albert. J. Louisiana M. Soc. **107:**452-453 (Nov.) 1955 [New Orleans].

Tietze's syndrome is characterized by a painful, nonsuppurative enlargement of a costal cartilage. The authors present the histories of four patients with this disorder. Relief followed surgical excision of the offending cartilage. In each patient, the prominent symptom was pain of long duration aggravated by local pressure and not relieved by rest. A palpable mass was also present in all four patients. Various treatments have been advocated including deep x-ray therapy, nitrogen mustard, local infiltration with procaine, corrective postural exercises and bed boards, and surgical removal of the involved cartilage. The authors excised the entire costal cartilage, including the chondrosternal articulation. The recent occurrence of a chondrosarcoma of the costal cartilage in one patient (not included in this report) impressed upon the authors the importance of surgical excision to exclude a malignant lesion. They believe that the surgical approach to Tietze's syndrome is the treatment of choice because of the positive identification of the mass, the simplicity of surgical excision, and postoperative symptomatic relief.

The Management of the Duodenal Stump in Gastric Resection for Technically Difficult Duodenal Ulcer. S. T. Chester and H. G. Bell. West. J. Surg. **63:**701-705 (Nov.) 1955 [Portland, Ore.].

Chester and Bell say that tube duodenostomy was described many years ago and has been successfully used by others, but it is usually considered a method of last resort, which entails a stormy postoperative course. On the basis of the histories of 10 patients, in whom they used tube duodenostomy for technically difficult duodenal ulcers, they demonstrate that this is a simple method that is both expedient and safe. None of their patients died as the result of the procedure. Hospitalization was somewhat prolonged in three patients due to prolonged drainage from or around the duodenostomy tube, but it was never longer than three weeks. The indications for the tube duodenostomy in this series were: (1) to expedite the operation in a poor risk patient; (2) as a safety measure when, because of technical difficulties, the duodenal closure was unsatisfactory; and (3) when the extent and degree of scarring and inflammation were such that closure of the duodenum was poor and leakage seemed inevitable. The stump was closed when possible with a single layer of Lembert sutures of no. 40 cotton. A no. 20 Robinson catheter was then placed into the duodenum between two sutures and anchored in position with a fine catgut suture. When feasible, the stump was turned into the peritoneum overlying the pancreas with a second row of interrupted sutures. The catheter and a Penrose drain were then brought out through a stab wound in the right flank and the intraperitoneal portion of the tube and drain was covered by the hepatic flexure of the colon and the greater omentum.

Saint's Triad (Hiatus Hernia, Gall Stones and Diverticulosis Coli): The Problem of Properly Directing Surgical Therapy. E. D. Palmer. Am. J. Digest. Dis. **22:**314-315 (Nov.) 1955 [Fort Wayne, Ind.].

Among 170 adult patients with hiatus hernia studied during the past four years, 24 (14%) instances of Saint's triad were encountered. There may have been more, because the patients were investigated only as their clinical situation dictated, without a routine survey for the triad. Fourteen of the 24 patients were men. Their ages at the time the full triad was diagnosed varied from 35 to 73 years. In 14 patients only one of the three lesions had been detected and treated during the first period of medical investigation. This first diagnosis had been cholelithiasis in 10 instances, diverticulosis in 3, and hiatus hernia in only one. Eighteen of the 24 patients were treated surgically, with a total of 30 operations. The first surgical effort was directed at the gallbladder in 16 of the 18 patients. Only one was cured and nine were not helped at all by cholecystectomy. Nine patients had a second operation, seven for repair of hiatus hernia. This time six were cured or helped. Because of recurrence of hiatus hernia, two patients had a third operation and one, a fourth. Colon surgery was done in only one case. Thus the results of cholecystectomy were poor, whereas the symptomatic help provided by the repair of hiatus hernia was fairly good. Comparison of the incidence of Saint's triad in the material under consideration with data from the literature suggests that, when a patient with hiatus hernia is found to have either gallstones or diverticulosis, there is an excellent chance that the third disease is also present.

Epigastric Hernia Simulating Gastrointestinal Tract Disease. F. P. Catanzaro. U. S. Armed Forces M. J. **6:**1360-1362 (Sept.) 1955 [Washington, D. C.].

A majority of patients with epigastric hernia are asymptomatic and unaware of its existence. At the hospital at the Lake Charles Air Force Base, Louisiana, 12 epigastric hernias were repaired in the course of three years, during which time a total of 96 patients with hernias of all types underwent operative procedures. Although these figures are not large enough to be significant statistically, they give some indication of the frequency of epigastric hernia and should serve to alert the examiner to its possible presence, particularly in patients with gastrointestinal symptoms. During the past year three patients gave histories suggestive of upper gastrointestinal tract disease and on physical examination were found to have an epigastric hernia. These hernias were repaired, resulting in complete relief of symptoms in each instance. The patients were troubled with epigastric pain and discomfort after meals and with occasional bouts of nausea and/or vomiting.

Recolonization of the Intestine with Living Coli Bacteria After So-Called Temporary Intestinal Sterilization. F. Zettler. München. med. Wchnschr. **97:**1527-1528 (Nov. 18) 1955 (In German) [Munich, Germany].

Resection of colon and rectum was performed on 194 patients at the surgical clinic of the University of Erlangen, Germany, between 1952 and 1954. To reduce the number of bacteria in the intestines, the patients, most of whom had carcinoma of the rectum, were given 7 gm. of phthalylsulfathiazole (Taleudron) daily for six days and 1 gm. of chlortetracycline (Aureomycin) daily for three days before the surgical intervention. A mild laxative was given preoperatively and the patients were placed on a low residue diet. The removal of the portion of the colon invaded by the carcinoma was carried out in one stage. After the operation the patients were given one ampul of a penicillin-streptomycin preparation (Supracillin) daily for five to seven days. There were less postoperative complications and a reduced operative mortality as compared with complications and mortality in patients who did not receive this preoperative and postoperative treatment. However, postoperative diarrhea, which occasionally was refractory to treatment, occurred in 32 (16.5%) of the 194 patients. There was a definite cause and effect relationship between this diarrhea and the destruction of the intestinal bacterial flora or a deficient restoration of this flora. Two patients died of enteritis caused by micrococci (staphylococci), and one of enteritis caused by streptococci. These experiences induced the author to combine the postoperative antibiotic therapy with the administration of "Colifer," a proprietary preparation of living lyophilized Escherichia coli, in doses of 10 to 15 cc. given orally in water, or the same dose was administered in 250 cc. of tepid water as an enema into the cecal fistula in patients in whom such a fistula was produced for the relief of the anastomosis. Early restoration of the reduced bacterial flora resulted from the administration of this Escherichia coli culture, which is of a high biological value and which prevents the overgrowth of resistant causative agents. Postoperative intestinal disturbances were no longer observed after the institution of the Colifer therapy. Combined treatment with antibiotics and Colifer is recommended for all surgical interventions on the colon.

Cutaneous Leiomyosarcoma with Lymphatic Spread: A Report of Two Cases. J. Levack and A. Dick. Glasgow M. J. **36:**337-342 (Oct.) 1955 [Glasgow, Scotland].

The first of the two patients was a 56-year-old man, who came to the hospital with a firm, superficial, slightly painful swelling on the upper and medial aspect of his right forearm first noticed as a firm, slightly tender nodule of the skin four weeks previously. The tumor was excised and found histologically to be a solitary cutaneous leiomyoma. At the second admission for a wider excision, a small painless nodule was found under the scar and the subcutaneous tissue contained two small nodules of tumor, which gave the appearance of leiomyosarcoma. Eight months later the patient was readmitted on account of pain in the scar region and was found to have a recurrence near the scar, which was hard, irregular, and indurated and appeared malignant. The previous scar and the recurrent tumor were excised along with a margin of normal skin. At one part the affected area appeared to be adherent to the deep fascia, which was also removed along with some underlying muscle tissue. The patient was seen at frequent intervals thereafter and remained well for nearly two years. He then presented himself with a painful lump in the right axilla of four weeks' duration, and the epitrochlear node was also enlarged. An interscapulothoracic amputation with clearance of all axillary glands was carried out; the main vessels were ligated and divided after resection of the clavicle. The neurovascular bundle was divided high in the root of the neck. The arm was removed with the pectoral muscles, the axillary contents, and the scapula. Histologically the axillary and epitrochlear lymph nodes were extensively infiltrated by leiomyosarcoma. The man was examined at frequent intervals and when last seen 22 months after the amputation, he was wearing a cosmetic prosthesis and appeared in good health. The second patient was a man, aged 32, who presented himself with a painful swelling on the right shoulder, one of the less common sites of leiomyoma. This and the pleomorphic structure of the tumor made the initial histological diagnosis more difficult. After prolonged study of the material from this case, several areas were identified that presented a resemblance to longitudinal smooth muscle fibers, and the tumor was considered to be a rather unusual and malignant form of leiomyoma cutis of the type described by Diss, in which pleomorphism was marked. The situation of the tumor in relation to the dermis certainly favors this diagnosis. The further course and the need for radical excision corroborated the diagnosis. The authors feel that solitary cutaneous leiomyomas may not be so rare as the literature would indicate and must be considered in the differential diagnosis of a superficial painful tumor. An accurate diagnosis can rarely be made without a biopsy, but if the histological diagnosis indicates undue activity and pleomorphism of the tumor then wide excision of the area must be undertaken.

NEUROLOGY & PSYCHIATRY

The Surgical Treatment of Epilepsy. L. A. Titrud, R. B. Tudor and V. R. Zarling. Journal-Lancet **75:**469-472 (Nov.) 1955 [Minneapolis].

If the epileptic patient has seizures that cannot be controlled medically and if these convulsions are found to originate constantly from the same circumscribed area of the brain, cerebral surgery may be advisable. The authors present the histories of seven patients who were operated on and state that such patients have a better than 50% chance of being cured of their epilepsy and about half of the others obtain some improvement. Careful diagnostic studies are required for selection of the suitable cases. Convulsive disorders should be detected in childhood so that proper therapy may be instituted before brain damage occurs. The candidates for surgical treatment have usually been studied and treated medically for more than a year or two unless they have unmanageable status epilepticus. Several electroencephalograms must be consistently similar; the localizing quality of the epileptic aura, the nature of the seizure, and the abnormal neurological findings should substantiate the electroencephalographic record of the focus. When craniotomy is done, a large area of the brain about the epileptogenic focus is exposed. An electrocorticographic study of the exposed cerebral cortex is done first. The electrodes that are placed over the brain surface serve to indicate the irritative focus. Frequently, meningeal scarring is visible at such a site. Small and deformed gyri or degenerated brain tissue may be apparent. Infrequently, a depth electrode may have to be used to localize a subcortical focus. If the involved brain area has an important function, such as the motor cortex, excision is not carried out, unless the severity of the convulsions outweighs the paresis that would result from surgery. If excision is done it should include the focus and extend into the white matter. After the excision an electrocorticographic survey should be made again to be sure no abnormal areas remain; if they do, these must be removed also. These patients usually have a satisfactory convalescence. They are given small daily doses of phenobarbital or Dilantin for about one year after surgery.

Factors Producing Ego Disintegration in the Aged. E. W. Busse, R. H. Barnes and L. D. Cohen. North Carolina M. J. **16:**528-532 (Nov.) 1955 [Winston-Salem, N. C.].

Depressive reactions are among the most frequent psychiatric disorders seen in the elderly. The factors producing these depressions seem an outgrowth of the person's perception of changes in his social and physical status, changes that threaten his self-regard. The second major psychiatric disorder in the elderly is senile dementia, an example of ego breakdown in which organic changes in the central nervous system may be important; but there is no consistent relationship between the clinical picture and the postmortem findings. Some of the disorders affecting hospitalized elderly people fall into the category of schizophrenic reactions rather than into the senile dementia group. Schizophrenic reactions in the elderly have generally been ignored. In addition to these more clearly defined types of break-

down, there occur varying degrees of disturbed behavior, which are often grouped under the heading "adjustment reaction of later life." The elderly person may become argumentative, hostile, withdrawn, and suspicious. Adjustment problems of this sort represent clinical examples of partial breakdown in ego functioning. The adjustment problems of elderly people demonstrate the importance of the individual's mechanisms for dealing with feelings about one's self and about others. Adjustment techniques become progressively more ineffectual, and the elderly individual is largely defenseless against the major stresses of of old age. He may then rely on memories and fantasies for his gratification and live in the past. The person with such defects is most vulnerable to the loss of external supports that come with age—loss of friends, relatives, and jobs. Bodily changes associated with aging, such as loss of physical beauty and attractiveness and motor efficiency, are other stress factors for the elderly. Neurophysiological impairment of the brain may result from a cerebrovascular thrombosis or hemorrhage or from the more subtle cause of failing circulation. Unfortunately, physical damage to the brain is seldom easily reversed. The ego is unable to evaluate either the "me" or the outside world. Autistic logic and denial, strongly clouded by unconscious factors, replace reality testing, and the individual is left largely defenseless. In commenting on the disorganizing effect of the fear of death, the authors say that the average elderly subject denies that he fears death itself. The fears of terminal pain, disfigurement, and dying alone or unattended are more pressing than death itself. Further knowledge of the causes of ego breakdown and utilization of what we now know can lead to both more effective mental hygiene for old age and more rewarding management of those already disturbed.

PEDIATRICS

Asthma in Children. F. H. Wright. J. South Carolina M. A. **51**:374-379 (Nov.) 1955 [Florence, S. C.].

Acute asthmatic attacks in children are accompanied by disturbances of pulmonary physiology. The form of the attack is consistent and predictable. Treatment is conducted by giving sympathomimetic drugs or aminophyllin to counteract spasm of the bronchial musculature; antibiotics or corticotropin or cortisone derivatives to decrease inflammatory reaction; and expectorants and humidified inhalations to decrease the viscosity of mucus. The cycle of mutually reinforcing anxiety that arises between parents and the afflicted child can generally be interrupted by reassurance, by amelioration of the asthma with drugs, or by transferring the child to a hospital. The factors that lead to asthma are varied and complex. Asthma can be viewed as the response of certain individuals to accumulated stress. The sources of stress vary from time to time and from individual to individual. A constitutional predisposition, probably genetically determined, must be assumed. Superimposed factors of infection, of physical or chemical irritation, of specific allergic response, or of emotional tension serve to activate the latent tendency. Appropriate long-term management must be guided by the relative importance of these factors operative in an individual child. The prognosis for asthma in children is generally good. For many children it is a temporary or infrequent disturbance that need not interfere with a normal life. Care should be taken that therapeutic regimens do not rob the asthmatic child of this opportunity. For the few in whom asthma becomes a chronic, disabling problem, attention to the emotional components of the illness are clearly indicated and usually require the services of a competent psychiatrist.

Cardiospasm in Children. W. L. Palazzo. J. M. Soc. New Jersey **52**:569-571 (Nov.) 1955 [Trenton, N. J.].

The author presents histories of two children with cardiospasm or achalasia, whom he observed during the last four years. The condition is uncommon but is not rare. The symptoms of cardiospasm are those of obstruction at the cardia. In the newborn infant, vomiting or regurgitation of uncurdled milk is noted. In older children vomiting of undigested food is suggestive. This may be intermittent. There is generally poor nutrition and a failure to gain weight. The sensation of hunger is usually preserved. Recurrent lower respiratory infections occur as food material overflows from the filled esophagus into the tracheobronchial tree. The roentgen findings are those of constriction of the esophagus at the cardia. Fluoroscopically there may be observed intermittent relaxation of the cardia, allowing small amounts of barium to pass into the stomach. Mild cases may show only slight dilatation of the esophagus. Later cases may show marked dilatation and elongation, with loss of peristaltic action. Filling defects in the esophagus are often seen, representing retained solid food material. Plain chest films may show an air and fluid containing sac in the mediastinum, projecting usually into the right side of the chest when the esophagus is more dilated and elongated. The first of the two children presented here had a relatively early case with only moderate dilatation of the esophagus. The second case was of longer duration, showing a markedly dilated esophagus, with bronchopneumonia resulting from the spillover of ingested material into the tracheo-bronchial tree. Cardiospasm should be thought of as a possible cause of vomiting in children, and children with frequent respiratory infections should be subjected to esophagography to investigate the possibility of a spillover syndrome associated with cardiospasm.

The Clinical Syndrome of Cor Pulmonale in Infancy. P. Brusca and G. Granata. Minerva pediat. **7**:1031-1035 (Sept. 8) 1955 (In Italian) [Turin, Italy].

Cor pulmonale in infants is rare. The authors' results of a long-term study of 100 children from a few days to 6 years of age with bronchopneumonia did not reveal a single case of frank acute cor pulmonale. The characteristics of the syndrome in infants do not differ essentially from those of the syndrome in adults. Arteriosclerotic process of the lesser circulation, intimal hypertrophy, and embolisms, all of which are common in adults with this syndrome, are exceptional in infants, but atelectases, disturbances caused by compression, and infectious and mechanical causes are more frequent in infants. Diagnosis of acute cor pulmonale can be made only if the following signs are present: (1) clinical findings of pulmonary congestion of abrupt onset, with dyspnea, cyanosis, and accentuation of the second pulmonary sound; (2) radiological findings of increase in the right side of the heart with enlargement of the shadows attributable to the large pulmonary vessels without evident impairment of the left ventricle; and (3) electrocardiographic signs of hypertrophy and dilatation of the right ventricle and atrium. A clear distinction is made by the authors between cor pulmonale and the cardiovascular impairment that occurs during the course of infectious or toxinfectious pulmonary diseases in infants. A diagnosis of cor pulmonale can be made in those infants in whom a true cardiovascular impairment caused by vascular or parenchymal alterations of the respiratory system is present together with the clinical, radiological, and electrocardiographic findings mentioned earlier. It should be ruled out in those infants in whom a cardiovascular impairment arises during the course of a pulmonary disease or a systemic disease localized to the lungs and is not the result of a vascular or parenchymal alteration of the respiratory system but the expression of a general toxic infection or metabolic derangement.

Contribution to the Problems of Diagnosis and Therapy in Infants with Stenosis of the Aortic Isthmus. G. Gruner and M. Herbst. Klin. Wchnschr. **33**:996-1002 (Nov. 1) 1955 (In German) [Berlin, Germany].

Clinical observations and autopsy findings are reported in 12 suckling infants with stenosis of the aortic isthmus proximal to the ductus arteriosus. Four of the infants were deficient in weight at birth; all of them were difficult to feed; they did not grow, were pale, and showed lung symptoms. The clinical aspect was frequently that of afebrile pulmonary congestion, swelling of the liver, pronounced pallor, and dystrophy. Rise in temperature and cyanosis occurred only in the final stage. Comparative determinations of blood pressure in the upper and lower extremities proved significant. The pulse of the femoral artery was found palpable in all the infants, but there were definite differ-

ences in pressure between the upper and lower extremities in infants with obliterated ductus arteriosus, in whom lower values were determined in the lower extremities. The same values as in the upper extremities, or higher values, were determined in the legs of infants with open or narrowed ductus arteriosus. Development of collateral circulation was revealed by autopsy in three infants only. One of these three, a 5-month-old infant, with the classical infantile form of stenosis of the aortic isthmus and with a wide-open ductus arteriosus showed symptoms that were pathognomonic of the adult type of stenosis only, i. e., difference in blood pressure, prestenotic hypertension, visible collateral circulation (paraumbilical arteries, diastolic collateral sounds, roentgenologic costal defects), and electrocardiographic left axis deviation. Complicating septal defect including persistent foramen ovale was absent in two infants only; abnormalities of segments of auriculoventricular valves and of semilunar valves, fibrosis of endocardium and myocardium, as well as other malformations of the organism were frequently observed. The unfavorable prognosis justifies the use of all modern diagnostic methods such as angiocardiography, aortography, catheterization of the heart, unipolar thoracic leads, and determination of circulation time. Surgical treatment under direct vision is likewise justified despite the much greater operative risk associated with stenosis of the aortic isthmus.

DERMATOLOGY

Cortisone and Corticotropin Treatment of Pemphigus: Experience with 28 Cases over a Period of Five Years. C. T. Nelson and M. Brodey. A. M. A. Arch. Dermat. **72:**495-505 (Dec.) 1955 [Chicago].

The aim of steroid therapy in a relentless, highly fatal disease like pemphigus should be, first of all, to relieve distress and prolong life. The existence of various complications may make it necessary to undertake corticosteroid treatment as a calculated risk, but even the most severely affected pemphigus patients can often be relieved of their incapacitating illness if certain precautions are observed. Continued hormone administration can then be planned with the hope that the disease may abate and ultimately reach a stage of natural remission that will permit withdrawal of the steroids. A clinical remission of this sort has been maintained for 25 months by one of 28 patients treated with cortisone and corticotropin from 1949 through 1954; 20 others require corticosteroids in varying amounts either daily or sporadically to keep the disease under control; and the remaining 7 are dead. One of the patients had pemphigus foliaceus; four of the others, all of whom had pemphigus vulgaris, had the vegetans variety and exhibited hypertrophic granulations in the denuded areas of skin; and three showed the clinical features of pemphigus erythematosus (Senear-Usher syndrome) at the onset of their illness. Patients whose adrenal glands are intact and capable of responding to stimulation by adrenocorticotropic hormone may be given either corticotropin or cortisone. Administration of cortisone by mouth, however, is the simplest form of therapy and is to be preferred. Oral treatment, in patients with severe disease, has more recently been supplemented by corticotropin given first intravenously during the early stages of treatment and then, as the disease responds, intramuscularly for a few days, after which the patient has been maintained on cortisone therapy by mouth alone. Hormone therapy was instituted regardless of conditions ordinarily thought of as contraindications to it, and once instituted it was interrupted or withdrawn only on the appearance of the most ominous complications. The daily dosage, which may range from 300 to 1,500 mg. or more per day in equivalents of cortisone for oral administration, should be gradually reduced until the minimal effective (suppressive) dose is reached. Perhaps the most encouraging feature of the long-term hormonal treatment of pemphigus is the fact that, once the disease is brought under control, it can be kept in remission with maintenance doses that sometimes amount to only a fraction of the original requirement. The patient should be aware of the hazards involved in treatment of this kind, and should make regular follow-up visits to the clinic or office, for only so can the effects of steroid therapy be accurately noted and the dosage properly adjusted. The principal side-effects seen in these patients, apart from thromboembolic accidents, were psychic disturbances, osteoporosis, and the reactivation of peptic ulcers. Two of the seven deaths resulted from major thromboembolic accidents during therapy and are considered to have been due to the treatment. Therapy in the other cases in which death occurred was probably inadequate. All but two of the survivors are able to pursue their daily activities without serious restrictions.

Clinical Evaluation of Hydrocortisone Ointment. J. F. Mullins and E. M. Shapiro. GP **12:**59-61 (Nov.) 1955 [Kansas City, Mo.].

The topical application of cortisone was found to be ineffective, but hydrocortisone was highly effective in certain dermatoses. Concentrations varying from 0.1 to 5% of hydrocortisone were used in petrolatum, petrolatum-lanolin, carbowax, or vanishing creams. At first the acetate form was used, but later, because of its more potent systemic anti-inflammatory effect, the free alcohol was investigated. The authors summarize their observations on 300 patients treated with hydrocortisone acetate and hydrocortisone free alcohol. Patients were instructed to apply the 1 or 2.5% ointment four times daily and, whenever possible, symmetrical lesions were compared. When there was no symmetrical involvement, this form of therapy was compared with the standard modalities. Many patients had previously received other treatment. The application of the ointment was continued for an average of from 9 to 13 days. Marked improvement was obtained in 177 patients, moderate in 78, slight in 34, and no improvement in 11 patients. The authors were impressed with the consistently better response of the dermatoses in the thin-skinned areas, such as the eyelids, the periauricular region, and the anogenital region. In certain cases, response to the 2½% concentration was superior to the 1% concentration in relief of itching, burning, weeping, and vesiculation. In many other cases the 1% concentration gave marked relief within 24 to 48 hours. Response was very satisfactory in contact dermatitis, eczematous dermatitis, and atopic dermatitis. Seborrheic dermatitis, psoriasis, and lichen planus were mostly located on the thin-skinned areas and gave a satisfactory response. Hydrocortisone ointment was effective as an adjunct in the treatment of vesicular dyshidrosis of the hands and feet. Particularly impressive was the initial response of patients with cutaneous infection with Candida albicans. In almost every case, there was marked relief of erythema and pruritus within 24 to 48 hours. The skin appeared normal at the end of five to seven days. However, if medication was discontinued at this time, a large percentage of the eruptions recurred. Hydrocortisone ointment is not a panacea; it may make the patient comfortable while other specific measures are brought into use. The authors found hydrocortisone ointment the most effective agent in relieving itching in pruritus of the anus, scrotum, and vulva.

Progressive Systemic Sclerosis: Visceral Manifestations in Generalized Scleroderma. W. N. Piper and E. B. Helwig. A. M. A. Arch. Dermat. **72:**535-546 (Dec.) 1955 [Chicago].

The clinical records and autopsy protocols of 31 fatal cases of generalized scleroderma selected from the files of the Armed Forces Institute of Pathology have been studied in an attempt to determine the course and degree of visceral involvement in patients with this condition. Interpretation of the observations must be qualified, because these cases all ended in death and because, although generalized scleroderma occurs chiefly in women, 25 of the patients were men. The onset of the disease was predominantly characterized by vague joint symptoms that appeared within the year preceding the recognition of other signs or symptoms of generalized scleroderma or concomitantly with it. Involvement of the skin, second in frequency to joint symptoms as the initial manifestation, began with swelling, followed by tightening or thickening of the affected area, and progressed until the skin was bound down tight in 87% of the patients, pigmented in 65%, indurated in 58%, and mottled or leathery in 23%. The entire course of the disease was characterized by a steady progression of systemic involvement and symptoms increasing in severity and number. The incidence of major systemic involvement was as follows: cutaneous, 100%, with the skin of the entire body being affected in 52%; joints, 93%

(clinical examination); cardiac, 90%; pulmonary, 90%; renal, 74%; and gastrointestinal tract, 64%. Visceral involvement preceded the cutaneous manifestations in some patients. Pain and discomfort of various types made sedation necessary in most instances. The specific cause of death in these patients was hard to determine because in most cases there was more than one factor to which it could be attributed. Cardiac conditions were present in nine, renal failure in five, cachexia in five, terminal complications in four, pulmonary insufficiency in three, hypertension in two, and duodenal ulcer with hemorrhage, esophagealpleural fistula, and sarcoma with metastases in one each. The duration of the disease in the 17 patients in whom it was accompanied by Raynaud's phenomenon was longer than it was in the other 14. No clinical or pathological evidence of systemic involvement was found in a supplementary study of autopsy material from 27 patients with lesions of circumscribed scleroderma in whom generalized scleroderma was not considered to have been the primary cause of death. Patients with circumscribed scleroderma, however, should be thoroughly investigated for signs of other systemic involvement. The term progressive systemic sclerosis, which was proposed by Goetz and which provides a better description of the clinical picture presented by patients with this condition than does the term generalized scleroderma, might well be used until the cause of the disease has been definitely determined.

Prednisolone Topically and Systemically: A Clinical Evaluation in Selected Dermatoses: Preliminary Report. L. Frank and C. Stritzler. A. M. A. Arch. Dermat. **72:**547-549 (Dec.) 1955 [Chicago].

Prednisolone and prednisone, formerly called metacortandralone and metacortandracin, are new synthetic hormones that possess greater anti-inflammatory effect and activity than cortisone or hydrocortisone and do not produce sodium and fluid retention or potassium depletion. Prednisolone in strengths of 0.25% and 0.5% was prepared for topical application in an ointment of petrolatum and liquid petrolatum. Hydrocortisone in a concentration of 1% in an identical base was applied to contralateral areas wherever possible or was alternated with the prednisolone to permit a comparative evaluation. The prednisolone ointment was effective only in conditions that respond to the topical administration of hydrocortisone; in most cases, however, the response to hydrocortisone was quicker and more apparent. The rapidity with which inflammation subsided was about the same whichever preparation was used, but the relief of pruritus secured with hydrocortisone was so striking that an investigation is now being made to see whether hydrocortisone has any direct antipruritic effect. Increasing the strength of prednisolone from 0.25% to 0.5% did not increase its therapeutic effectiveness. Nine of the 256 patients in this series found prednisolone irritating when used topically, probably because the prednisolone ointment acted as a primary irritant on inflamed skin. Hydrocortisone was then substituted for prednisolone on the same areas and was well tolerated. The systemic administration tests showed that prednisolone is an effective and highly active anti-inflammatory corticosteroid for dermatological use. The dermatological spectrum of conditions responsive to prednisolone seems to be very much like that of hydrocortisone. An initial dose of 40 mg. seemed to be therapeutically effective in almost all patients. The maintenance dose averaged from 15 to 20 mg. daily. Patients who had been on a maintenance dosage of 80 mg. of hydrocortisone were able to substitute 20 mg. of prednisolone with no lag period or exacerbation of symptoms, showing that prednisolone is approximately four times as effective as hydrocortisone. Side-effects were varied, with about half the patients experiencing a feeling of well-being and an increase in appetite. Abdominal pain, complained of by six patients who were receiving a dosage of 40 mg. of prednisolone, diminished when the dosage was reduced. A moon face was produced in five patients. Only two patients were unable to continue on prednisolone therapy, one because of severe depression and the other because of severe epigastric distress and heartburn. The fact that prednisolone rarely leads to hypertension or sodium and fluid retention and that patients can be treated with it without any need for dietary restrictions is a decided clinical advantage.

PATHOLOGY

Coronary Disease: A Pathological Study. P. J. D. Snow, A. M. Jones and K. S. Daber. Brit. Heart J. **17:**503-510 (Oct.) 1955 [London, England].

The authors reinvestigated the relationship between coronary artery occlusion and myocardial infarction by the best available techniques for the postmortem study of both arterial and myocardial lesions. Twenty-five hearts from patients with clinical coronary disease were subjected to detailed postmortem examination, including coronary injection and comprehensive histological examination of the myocardium. The concept of the prevention of infarction by the development of collaterals concomitantly with gradual narrowing was not borne out. On the contrary, almost all occlusions (even in greatly narrowed arteries) gave rise to infarcts, and although collaterals developed they did not prevent infarction. Recanalized occlusions appear to be capable of transmitting a functionally significant blood supply, for if they reocclude new infarction follows. Not only do major occlusions almost invariably cause infarction but in addition a single occlusion frequently gives rise to more than one infarct. In fact, extension of an infarct into adjacent ischemic zones is a commonly observed pathological event, and this occurs without further coronary occlusion. This tendency for an infarct to extend exists for a period of three to eight weeks after the original infarct, and this period corresponds closely with the time required for the full development of collateral vascularization of the ischemic area. It is reasonable to conclude that the collateral circulation, when fully developed, plays an important part in preventing the extension of infarction by revascularizing adjacent ischemic areas of myocardium.

Serologic Test for Cancer (Preliminary Report). E. B. Povoa. Rev. brasil. med. **12:**222-224 (April) 1955 (In Portuguese) [Rio de Janeiro, Brazil].

A new test for a serologic diagnosis of cancer and for a differential diagnosis between benign and malignant tumors is presented. The technique is that of a quantitative complement fixation, using an antigen prepared from cancerous tissues. Normally the blood serum contains this anticancer cytotoxin, which fixes the complement in the presence of a cancerous antigen and which is greatly diminished or missing in the blood serum of patients with cancer. The titer of normal concentration of anticancer cytotoxin in the blood serum is 500 units for each cubic centimeter of the serum. For interpretation of the results of the test the following titers are given: titers of 500 units of cytotoxin for each cubic centimeter of blood serum are normal; titers between 240 and 500 units for each cubic centimeter of blood serum are found in patients with benign blastoma or patients with cancer who are improved after irradiation, hormone treatment, or antireticular cytotoxic serum, as well as in persons predisposed to cancer; and titers between 0 and 240 units of cytotoxin for each cubic centimeter of blood serum definitely show presence of cancer. Titers of anticancer cytotoxin are very low in leukemias, which fact shows malignancy of leukemia. Results of the tests were proved by histopathological studies. Syphilis and tuberculosis do not interfere with the results.

Morphological Changes of the Erythropoietic System in the Presence of Tumors. E. Korinth. Blut **1:**161-164 (Sept.) 1955 (In German) [Munich, Germany].

Neoplastic diseases can influence the blood in various ways. Extensive metastases within the bone marrow may cause anemia by displacement, but anemia may also be produced by impairment of the erythropoiesis as the result of toxic products of metabolism or of disintegration. These toxic products may cause changes in the peripheral blood by causing a more rapid and increased destruction of the mature erythrocytes, but it can also cause changes in the bone marrow. The studies reported in this paper are concerned with the morphological changes in the cells of the erythropoietic system in the bone marrow in patients with tumors. The author presents data on 12 patients with various types of neoplastic disease. The majority of these patients had

a more or less severe hypochromic anemia in the peripheral blood. The sternal bone marrow showed the following changes: 1. There was vacuolation of the nuclei of many preerythroblasts and macroblasts. 2. There was lack of homogeneity of the chromatin. The chromatin of the nucleus showed varied density and irregular distribution; frequently it was arranged in gross strata. 3. The nucleus showed marginal arrangement of the chromatin, the so-called hole-form of nucleus, and this was associated with uneven distribution, and the chromatin picture was atypical as regards the status of maturation. It cannot be definitely ascertained whether these changes represent the same process, which is generally known as hyperchromatosis of the nuclear wall and which represents a step in the involution of the nucleus. 4. There is clumping of the chromatin in the nucleus. The chromatin often appears eccentrically located as a homogeneous mass, whereas the cellular membrane is at the normal site. All cells in the erythropoietic system may show these changes. Morphologically these cellular changes can be differentiated from the pictures of karyorrhexis in anemias that have a different pathogenesis such as megaloblastic anemia and hemorrhagic anemia. The structural cellular changes in the anemias that accompany neoplastic diseases suggest that toxic factors either abolish or block the process of erythropoiesis. The nuclear changes may be regarded as the sequel of a disturbance in karyokinesis and in cellular development and maturation. It was impossible to ascertain whether the structural changes in the individual cell are reversible. The bone marrow changes proved to be reversible.

RADIOLOGY

The Dangers of Bronchography in Pulmonary Tuberculosis. K. M. A. Perry. Brit. J. Tuberc. **49:**284-292 (Oct.) 1955 [London, England].

The author mentions several attempts at outlining the bronchial tree by an opaque medium. While about 70% of the iodized oil, Lipiodol, is expectorated three or four hours after its injection, the rest remains in the lung indefinitely and little is absorbed. "Plugging" of bronchioles and alveoli with the oil and resulting pulmonary collapse has been observed. Another disadvantage of the retention of Lipiodol is that it produces x-ray shadows for many years afterwards. A newer opaque medium, Dionosil, in both watery and oily solution, is absorbed in the lung and is excreted by the kidneys. It does not, however, give quite such a good definition as Lipiodol and is still an iodide preparation. The older generation of physicians was aware that pulmonary tuberculosis tended to be activated by iodine and its derivatives and so was careful to avoid giving it to patients with this disease. In recent years this opinion has tended to be disregarded and even denied and bronchography has, in some places, been carried out in patients with chronic pulmonary tuberculosis, particularly preparatory to segmental resection. At one London Chest Hospital it was demonstrated that bronchography demonstrates a degree of segmental localization not obtainable by other means. The author, however, presents two patients in whom tubercle bacilli appeared in the sputum after bronchography with oily mediums. In three other cases, tuberculous bronchopneumonia was precipitated by the investigation. This evidence supports the theory that iodine activates tuberculosis and shows, therefore, that bronchography is a dangerous investigation in patients with that disease.

Roentgen Abnormalities of the Large and Small Intestine Associated with Prolonged Cathartic Ingestion. N. Heilbrun and C. Bernstein. Radiology **65:**549-556 (Oct.) 1955 [Syracuse, N. Y.].

The authors describe clinical and roentgenologic observations on the colon of nine patients, who had taken irritant or drastic cathartics daily over a period of at least 15 years. The roentgenologic changes simulated enterocolitic lesions. The early changes were seen in the cecum and ileocecal valve. As they became more severe and diffuse, they extended proximally to involve the terminal ileum and distally to involve the colon as far as the sigmoid. Even though the roentgen findings suggested a colitic or enterocolitic process, the clinical histories of all these patients were completely devoid of diarrhea, crampy or frequent bowel movements, or bloody discharge. Direct examination of the rectum and sigmoid revealed no evidence of active or old inflammatory disease suggestive of ulcerative or amebic colitis. At times the mucosa was described as somewhat edematous but it did not bleed easily nor was it unduly reddened. Melanosis coli was occasionally seen when cascara was used alone or in combination with other drugs. Roentgenologic examination revealed in the mild cases that the cecum was somewhat foreshortened and conical. The valve had lost its normal beak-like appearance and the lips were shortened and gaping. When the changes were more severe, the colon distal to the cecum became tubular, with diminished haustrations. In the more severe cases, the preliminary plain film studies showed the abnormal tubular outline of the gas-filled intestinal segments. On fluoroscopic examination the rectal capacity was not found to be diminished and there was no evidence of significant shortening or rigidity of the rectum and sigmoid. The author presents the clinical histories of six of the patients, and points out that the active principles of the cathartics used act directly upon the mucosa of the small and large intestine. Their irritant action reflexly stimulates increased muscular activity and tonus. With high levels of tonus, the motility of the intestine is seriously impaired. In persistent hypertonicity, the motility patterns become incoordinated and reduced in amplitude and frequency. Such states lead to constipation from slowed intestinal transport. Thus a vicious circle is established by the need for the continuous daily ingestion of a mucosal irritant strong enough to stimulate the intestinal musculature reflexly to overcome the incoordinated muscular action due to hypertonicity. The majority of the proprietary mixtures used were composed of combinations of the milder emodin and the more drastic resinous cathartics. Others contained the irritant chemicals, calomel or phenolphthalein, with one or more of the vegetable irritants. It is suggested that the continuous overdosage for so many years is responsible for the roentgen manifestations, namely, the simulation of enterocolitis, which must be differentiated from inflammatory disease affecting the small and large intestine as well as from colonic dysfunction or irritable colon.

The Palliation of Bronchial Carcinoma by Radiotherapy. G. Blanshard. Lancet **2:**897-901 (Oct. 29) 1955 [London, England].

The investigations described were undertaken to determine what forms of bronchial carcinoma are best suited for palliative roentgen therapy. The patients were seen at the radiotherapy departments of two London hospitals between August, 1953, and January, 1954. Only those receiving palliative x-ray therapy were accepted. The diagnosis was histologically confirmed in 35 of 69 patients, and the analysis of the effect of radiotherapy was restricted to these 35. Roentgen therapy in most patients was applied to anterior and posterior chest fields, but in a few patients additional parts were employed. Seven patients were treated with the aid of grids. The average over-all course was 2,942 r, at 220-250 kv. and 10-17 ma., spread over 17 treatments given during 31 days in hospital. The dosage differed at the two centers, one giving an average of 3,722 r in 23 treatments, the other 2,161 r in 12 treatments. Otherwise there was no significant difference in the treatment received. Some patients received antibiotics in addition to the x-ray therapy. In most patients erythema and pigmentation developed at the site of irradiation. Some had anorexia and slight nausea, but none had radiation sickness. The various types of response are illustrated on the basis of case histories. Obstruction of the superior vena cava was relieved in 83% of the patients, cough in 76%, dysphagia in 75%, hemoptysis in 64%, and dyspnea in 58%. After treatment 60% of patients had improved as regards their general condition, 49% were able to live independently, and 17% returned to work. The most effective course was an average dose of 2,161 r given in 12 treatments. Higher dosage and longer treatment produced no better results. Squamous-cell tumors did not show such good results as did other histological types. Upper-lobe growths responded slightly better than lower-lobe growths.

BOOK REVIEWS

The Body Fluids: Basic Physiology and Practical Therapeutics. By J. Russell Elkinton, M.D., Associate Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, and T. S. Danowski, M.D., Renziehausen Professor of Research Medicine, University of Pittsburgh School of Medicine, Pittsburgh. Cloth. $10. Pp. 626, with illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1955.

This volume is an attempt by the authors to cover the subject of disturbances of body fluid dynamics. They accomplish this task in a commendable manner. Both authors are qualified by experience to undertake this work, and they have thoroughly reviewed the literature. The bibliography is complete concerning both the fundamental work on fluids and the clinical applications of experimental findings. The book is complete in that it covers the subject well. There is a chapter on paleochemistry and comparative physiology that is interesting, of great teaching value, and delightful to read. Other chapters cover basic principles of fluid behavior. Electrolyte patterns in health and disease are treated along with studies in normal and disease processes. Excellent chapters on cardiac and renal failure, diabetes, and cirrhosis are included. The chapter on functions of the adrenal cortex is excellent and up-to-date. The main criticism of this book is that some of the diagrams are too complicated, although most of them are excellent. The format is pleasing. This book fills a vacancy in physiological, medical, and surgical libraries. It is heartily recommended for medical students and for any internist, cardiologist, or surgeon who is treating patients, for it is one of the best contributions to medical literature in recent years.

Recent Advances in Radiology. By Thomas Lodge, M.B., Ch.B., F.F.R., Consultant Radiologist, United Sheffield Hospitals, Sheffield, England. Third edition. Cloth. $10.50. Pp. 358, with 182 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6; J. & A. Churchill, Ltd., 104 Gloucester Pl., Portman Sq., London, W.1, England, 1955.

The compiler of this volume, an honorary editor of the British Faculty of Radiologists, was invited by Dr. Peter Kerley to carry on the highly valued series the first and second editions of which Dr. Kerley had so ably prepared in 1931 and 1936. Since then the complexion of the offering has undergone a profound change, properly noted by the present author in the preface. Actually "established practices" rather than "advances" would be more descriptive of the radiological material that has been presented. The term "recent," which survives in the title, does so entirely by virtue of the indulgence that Mr. Lodge has requested of his readers. On its 24th birthday this book has become what its writer describes as a general textbook of radiodiagnostics intended for radiologists engaged in general hospital practice. Its 10 chapters deal with various aspects of the clinical application of radiological principles and methods. The literary style is smooth, clear, and pleasing. The reproductions of roentgenograms are excellent, particularly the cerebral angiograms, and there is a spectacular figure depicting a pulmonary bleb associated with spontaneous pneumothorax (page 236).

It is unfortunate, since the book is offered under the frankly misleading designation of a description of procedures and practices that have lately come into use, that the discussions presented in nearly every chapter are even now subject to revision, for the present flavor of radiological thinking and performance are not conveyed to the students for whom this textbook was written. Detailed references are made to 416 medical writings, only 15 of which are as recent as 1953. Many promising contributions to the clinical practice of diagnostic radiology have appeared in the recent past, with the result that scope of the specialty has been expanded materially. A few of the regrettable omissions that may be cited are: intervertebral disk puncture, the new concept of ankylosing spondylitis, the discovery of numerous peptic ulcers in infants and young children, recent descriptions of volvulus of the sigmoid and cecum (unmentioned, although intussusception is presented in great detail), splenoportography, pulmonary sequestration, and intramedullary nailing. If one seeks up-to-the-minute presentation of what diagnostic radiology has to offer to clinical medicine, this book will prove to be disappointing. As a textbook of general radiological diagnosis for hospital radiologists, it does not provide adequate coverage of all problems that are commonly encountered.

Shearer's Manual of Human Dissection. Edited by Charles E. Tobin, Ph.D., Associate Professor of Anatomy, University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Third edition. Cloth $6. Pp. 287, with 78 illustrations. Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36; 95 Farringdon St., London, E.C.4, England, 1955.

In this new edition of a guide to an orderly display of the structures of the human body the editor has again made a good effort to discriminate between the more important and the less important structures by the use of boldface type. Very few changes in figures or text have been made from the former edition. However, the figures have been much better reproduced, the general appearance of the book is improved by the use of a better grade of paper, and several errors have been corrected. While some regions require less ample directions than others, some structures may be overlooked or resected before they are observed. For example, the superclavicular nerves will be severed when the clavicular incision is made in the pectoral region. Also, no mention of the sympathetic trunk is made when the dissection of the neck in the region of the carotid sheath is undertaken. Furthermore, some confusion may be evident in regard to the terms extensor and flexor regions of the thigh as used in the text. In general, this manual has attempted to combine brevity with clarity, and the editor has been successful in his presentation of a guide for a course that has been reduced in time in recent years.

The Principles and Practice of Surgical Nursing. By D. F. Ellison Nash, F.R.C.S., Assistant Surgeon, St. Bartholomew's Hospital, London, England. Cloth. $7. Pp. 1007, with 371 illustrations. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2; Edward Arnold & Co., 41-43 Maddox St., London, W.1, England, 1955.

This book was written to provide the nurse with a basis of understanding the "why" of the procedures she is to perform and to provide sufficient information for her to pass her examination. Any author who has attempted to write a general textbook of this type realizes the Herculean task it entails. Reasonable dogma must be used to impress on the student as many conditions and methods as possible. The hypercritical practitioner might disagree with a point here and there, but these points are generally minor. This book is well organized and interestingly written. It can be recommended both as a reference book and as a textbook.

Medical Support of the Army Air Forces in World War II. By Mae Mills Link and Hubert A. Coleman. Department of the Air Force, Office of the Surgeon General. Cloth. $7. Pp. 1027, with illustrations. Superintendent of Documents, Government Printing Office, Washington 25, D.C., 1955.

This book is an important contribution to military medicine. Beginning with the origins of an Air Force medical service in World War I, it describes the growth and present status of the School of Aviation Medicine, aeromedical research and development, air evacuation, and the medical support of air combat in various theaters of operations in World War II. It is well illustrated and has an index and a glossary. It will be of interest chiefly to flight surgeons and medical historians.

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

QUERIES AND MINOR NOTES

KELOIDS FOLLOWING THYROIDECTOMY

To the Editor:—*What is the cause and treatment of thickened and painful thyroidectomy scars? My patient has had three excisions of the scar because of thickening and stinging sensations. Repeated x-ray treatments beginning the day of excision were tried but failed to prevent recurrence. Kutapressin and Alidase injections gave only partial cure by lessening the congestion and stinging sensations. At operation of thyroidectomy the skin and fat were dissected separately from the platysena myoides muscle. Various methods of suturing were used, including fine nylon subcuticular but the condition recurs.*

M L. Raymond, M.D., Johnstown, Pa.

Answer.—Thickened and sometimes painful keloids are quite common in thyroidectomy incisions in children and young adults. It is rare that this complication occurs in people in middle age or beyond. There is no way that such a reaction can be completely prevented, because it is the result of a type of healing characteristic of younger people. Sometimes x-ray will seem to shorten the course of the keloid and cause it to flatten out earlier. Sometimes it seems to be of value in preventing it. Re-excision of the scar usually results in the patient having to start all over again with a new keloid. With the passage of time, the raised redness and the stinging sensation will disappear, and it is better just to use reassurance during this period. Later in life if the scar is too wide, it can be excised.

EXPOSURE TO TRICHLOROETHYLENE

To the Editor:—*At a manufacturing plant, metals are dipped in trichloroethylene, which is used as a degreasing agent. What are the possibilities of this chemical producing a chronic cough and bronchospasm in workers exposed to its fumes? What precautions should be taken by employees handling this substance?*

M.D., New York.

Answer.—Trichloroethylene is a distinctly toxic agent, but its characteristic manifestations do not include a "chronic cough and bronchospasm." These features have been reported, and currently some belief is that they foremostly may be attributed to additives to trichloroethylene for stabilization purposes. The prime action of trichloroethylene is upon the kidneys and liver, but the early action is of narcotic character leading to a state closely resembling ethyl alcohol intoxication. Instead of constituting a bronchial irritant, trichloroethylene, like chloroform, may possess properties leading to a sedative influence on the respiratory tract. Since trichloroethylene is a recognized injurious industrial agent, due protection should be provided by the employer. The maximum allowable concentration is 200 ppm of air. Procurement of tolerable atmospheric concentration may require the installation of appropriate exhaust systems.

WATERPIPE SMOKING AND LUNG CANCER

To the Editor:—*With the controversy on the possible cause of carcinoma of the lungs by cigarette smoking I would like to know if there has been a study of cigarette smokers in Turkey who use a waterpipe (nargileh) exclusively.*

W. Bergmann, M.D., Oakland, Calif.

Answer.—The nargileh of Turkey, as the hookah or kalian of Persia and other forms of waterpipes, is generally used with a bowl in which tobacco, hemp, or even opium may be burned, rather than with a paper-covered cylinder of tobacco or cigarette. The type of tobacco as well as the manner of its preparation, the presence of paper or other materials, the force with which the smoke is sucked, and the depth to which it is inhaled differ widely from that of cigarette smoking. (Bogen, E.: The Composition of Cigarets and Cigaret Smoke, *J. A. M. A.* **93**:1110 [Oct. 12]1929). Studies in other countries indicate that pipe smokers do not have the excess lung cancer mortality that is noted among cigarette smokers (Sadowsky, D. A.; Gilliam, A. G., and Cornfield, J.: The Statistical Association Between Smoking and Carcinoma of the Lungs, *J. Nat. Cancer Inst.* **13**:1237 [April] 1953). This probably applies to the users of the nargileh, though no direct studies have been made of it. Since cigarettes are also widely used in Turkey, and vital statistics there are incomplete, the relatively lower respiratory cancer rates reported among the Turks (Hoffman, F. L.: The Mortality from Cancer Throughout the World, New York, Prudential Life Insurance Co., 1915, p. 701) cannot be attributed to the use of the nargileh.

BACTERICIDE FOR SWIMMING POOL

To the Editor:—*Is chlorination, or any other chemical agent, in eye-tolerated concentration, necessary for prophylaxis against any pathogenic organism likely to be found in a private, little used, swimming pool, which has constant inflow and outflow?*

M.D., New York.

Answer.—If the pool is a natural outdoor pool, or if it has been artificially constructed, and the source of water is untreated river or lake water, a sanitary survey should be made to determine the possibility of the source water carrying contamination into the pool. If the pool is using treated city water and has very light bathing loads, plus continuous flow, these conditions minimize the necessity for water purification. The diluting volume or the rate of inflow to outflow is very important in either a natural or an artificial swimming pool. More than 500 gal. of fresh water per bather per day may eliminate the necessity for disinfection, but with less than this volume the water in the pool will probably require treatment. If the pool water is shown to be contaminated by bacteriological test, it should be treated with chlorine, hypochlorite, or other halogen compounds. Chlorine in concentrations of 0.5 to 1.0 ppm is an effective bactericide for Aerobacter aerogenes, Escherichia coli, and the various species of Salmonella and Shigella. The official report of the American Public Health Association on swimming pools states that "public swimming pools must maintain a residual (excess or available) chlorine in the water at all times when the pool is in use of not less than 0.4 ppm or more than 0.6 ppm." This residual range is effective against pathogenic bacteria and will not cause any eye discomfort to swimmers.

HIGH BLOOD SUGAR LEVEL

To the Editor:—*An obese woman 63 years old has diabetes mellitus. In spite of a diabetic diet and 60 units of protamine zinc insulin daily, her blood sugar level still is around 236 to 259 mg. per 100 cc., although a urinalysis often is negative for sugar. Is there any danger from such high dosage of insulin over a long period of time?*

Julian Movohan, M.D., Oakwood, Ohio.

Answer.—There is no danger in the prolonged use of protamine zinc insulin in the dosage mentioned, or even higher doses, provided the fasting blood sugar level is determined regularly at intervals of a few weeks and is not allowed to fall below levels of 150 mg. per 100 cc. Certainly weight reduction would be of prime importance in this case, and as weight is lost a reduction in insulin requirement is to be expected. If ordinary measures directed at weight reduction are not successful, it is likely that the patient would benefit greatly by a period of hospitalization during which time the realities of a weight-reducing diet could be enforced on her. In this situation the decrease in insulin requirement might conceivably be abrupt and striking.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

ASPERMIA DURING INTERCOURSE

To the Editor:—*A 36-year-old man, married five and a half years, has testes and penis of normal size, and his semen was found to be normal. He has been having pollutions every few weeks when asleep but when having intercourse he cannot ejaculate any sperm despite normal erection lasting 10 minutes. Repeated Huhner tests and examination of the condom worn during coitus never revealed any sperm. How can he be helped to have children?*

M.D., New York.

This inquiry was referred to three consultants, whose respective replies follow.—Ed.

Answer.—To aid this patient toward fatherhood, the cause of the pollutions should be removed, if possible. Examination should be carried out for local sources of irritation. The condition is frequently met with in neurotic individuals. Treatment may be divided into medical and psychiatric. The medical may be prophylactic and active. Under prophylactic may be included the removal of any cause of irritation, such as coitus interruptus, chronic masturbation, or excessive riding. Active treatment may include instillations of weak silver nitrate solution, sedation, hydrotherapy, and electrotherapy. Prostatic massage may be employed with discretion. The essential elements of psychotherapy consist of sex education and advice to rid the patient of conflicts or fears he may be entertaining in regard to marriage. If the results of such therapy are poor, artificial insemination should be considered. The patient should wear a sulfur-free prophylactic when retiring for the night. The sperm may then be retrieved from this source and used in artificial insemination.

Answer.—The condition here described represents an uncommon but well-recognized variety of partial impotence. Since nocturnal emissions occur, it may be assumed that there is nothing intrinsically wrong with the reflex neuromuscular mechanism of ejaculation. With a view to other causes, the patient's general health, hygiene, and endocrine status should be investigated. In most cases of impotence, complete or partial, a psychogenic factor is predominant and so a cure can rarely be accomplished without adequate psychotherapy. As long as normal physiological performance remains impossible, the following plan of treatment might be tried. The couple should abstain from intercourse during the week preceding the wife's calculated ovulation time. When that date approaches, the husband on retiring each night should put on a condom, "fish-skin" rather than rubber, and use an elastic band to hold it in place. Sooner or later a nocturnal emission will occur at or near the fertile point in the wife's cycle. If the husband is properly instructed, he should have no difficulty in drawing the semen up into a syringe and depositing it on the cervix.

Answer.—The patient referred to evidently owes his sterility to a retrograde ejaculation of his semen into the bladder after sexual intercourse. The simple way of determining this is to examine his voided specimen of urine for spermatozoa obtained immediately after coitus. If spermatozoa are found in the voided specimen of urine, the centrifuged specimen of urine containing spermatozoa can be used for artificial insemination provided husband and wife consent to this procedure. But before resorting to artificial insemination, a urologic and psychiatric assessment of the husband's condition is advisable because local conditions around the internal sphincter of the bladder can be cleared up by urologic methods of treatment on the one hand, while spastic conditions based on psychic inhibitions can be relieved through psychiatric therapy. Before undertaking the artificial insemination with centrifuged spermatozoa, the husband should take 30 grains (2 gm.) of bicarbonate of soda three times daily after meals for three or four days before the next sexual relation session in order to alkalize his urine. He is instructed to void before coitus and immediately after. This specimen containing spermatozoa is centrifuged, and the sediment with the small amount of urine is injected into the vagina. The wife should take a douche of Ringer's or Locke's solution to assure the alkalinity of the injected spermatozoa. It is understood that before subjecting the woman to artificial insemination a complete sterility investigation has shown her to be potentially fertile. Success has been reported in two cases in which this condition was found and the method of insemination described above was employed. The first report by Fischer and Coats appeared in *Obstetrics and Gynecology* (4:352 [Sept.] 1954).

KERATOCONUS

To the Editor:—*What information have you on cyclodialysis surgery for keratoconus? My patient has eight pair of glasses from eight specialists and cannot see with any of them.*

M.D., Michigan.

Answer.—Keratoconus is a condition in which the cornea, instead of being symmetrically curved, is cone shaped, thus giving rise to marked astigmatism. When the condition is severe, there may be tears in Descemet's membrane and marked thinning of the cornea. Vision may be markedly decreased, and ordinary lenses do not compensate for the irregular curvature. Contact lenses substitute a symmetrical surface and are frequently valuable in improving vision. There is no medical treatment for the condition. If vision cannot be corrected to more than 20/200 with contact lenses, keratoplasty (corneal transplant) should be done. Results with this are frequently unusually good. It is not believed that cyclodialysis has been recommended for this condition, and it is questionable whether it would be effective.

HYSTERECTOMY

To the Editor:—*What standpoint should be taken in the question of total versus subtotal hysterectomy in young women, below age 35, in cases of benign uterine pathology? If total hysterectomy has to be done in all cases, is it advisable to leave one ovary in these young women, and if so, has the risk to be accepted that this ovary may become the cause for future trouble?*

M.D., New York.

Answer.—When a hysterectomy is indicated, a complete or total hysterectomy should be done regardless of the age of the patient. The cervix alone is of no value physiologically or anatomically. In addition to carcinoma of the cervix or endocervix, many other pathological processes arise in the cervix, such as cervicitis, endocervicitis, erosion, polyps, and cysts. The coexistent discharges that accompany these lesions are a nuisance to most women, and a considerable percentage of the gynecologists' time is spent in treating them. Leaving the cervix as a means of support of the pelvic fascia is unnecessary and may be a mistake. If the fascia is not relaxed it is not necessary to leave the cervix to support it; if the fascia is already relaxed leaving the cervix prevents suturing the broad and uterosacral ligaments to support the pelvic structures and would more than likely produce cervical prolapse. Fastening the round ligaments down to the stump of the vagina not only does not add to the support but frequently makes a tense, painful, hammock-like band across the pelvis about which patients often complain. The depth of the vagina is about the same with abdominal hysterectomy whether or not the cervix is removed. In vaginal hysterectomy with plastic repair, the depth of the vagina depends primarily on the presence or absence of an enterocele. If the enterocele is corrected from below, it necessarily shortens the vagina. The vagina is so pliable that, if the ovaries are functioning, any small variation in vaginal depth is soon corrected as soon as sex life is reestablished. Removal of the ovaries accounts for most of the vaginal atrophy and shrinkage. When placing the suture that closes the pelvic peritoneum, if one inverts and loosely sutures each ligament as it is encountered from side to side and loosely includes the vaginal cuff, excellent pelvic support is obtained with pliability. One almost never sees dyspareunia or vaginal prolapse following this method. The question of removing ovaries is controversial. Age should be the least important consideration in deciding whether to remove the ovaries. One often sees women of 50 and 55 years still menstruating. The ovaries should always be examined carefully, cutting them open end to end in questionable cases. Often the rather large ovary is the only normal one, the opposite one being atrophic. If both ovaries look normal, they should both be left.

Great care should be used in maintaining the ovarian circulation. One must risk the rare possibility of an ovary becoming malignant or causing trouble in later life. If endometriosis is not already present, it should not develop after removal of the uterus, although it may get worse if already present unless both ovaries are removed. In the woman aged 50 or over, one must use individual judgment about removal of the ovaries.

OSTEITIS DEFORMANS

To the Editor:—*What effect have cortisone, hydrocortisone, and metacortone on osteitis deformans? Are there any other drugs of value in this disease?* *M.D., Pennsylvania.*

Answer.—In osteitis deformans (Paget's disease), local bone destruction of unknown etiology elicits secondary compensatory overproduction of thickened, deformed, highly vascularized bone. This disease is usually asymptomatic but may produce bone pain, deformity, deafness, headache, heart failure, and renal stones. In one paper (*Tr. A. Am. Physicians,* **68**:238, 1955) the authors report experimental evidence that corticotropin (ACTH) and cortisone administration to patients with severe osteitis deformans produces alterations in calcium balance, a fall in serum alkaline phosphatase level, changes toward normal in biopsies of involved bones, fall to normal of markedly elevated cardiac outputs, and prompt relief of bone pain and headache. Unfortunately the large doses of corticotropin or cortisone that may be necessary to suppress osteitis deformans may be expected to have the usual incidence of complications of adrenocortical hyperfunction such as osteoporosis with vertebral fractures, lowered resistance to infection, psychosis, and peptic ulcer. It remains for future investigation to outline the limits of clinical usefulness of cortisone in osteitis deformans. To provide building material for maximum compensatory repair of involved bones in osteitis deformans vitamin C 500 mg. daily, vitamin D 50,000 units twice weekly, and two to three glasses of milk daily have been used. In certain instances this safe therapeutic regimen has produced gratifying relief of bone pain.

CANNED FOOD

To the Editor:—*How may I determine, after opening a can that is not bulging, if the contents will be harmful when eaten? Under certain conditions canned goods are kept in the house for a long time.* *M.D., Pennsylvania.*

Answer.—Commercially canned food will keep in good condition almost indefinitely and can be used without fear as long as the container shows no evidence of deterioration, such as bulging ends and/or excessive rusting. The heat treatment to which all canned foods are subjected destroys any spoilage bacteria present in the food. The permanent seal on the can prevents reinfection of the food by any such bacteria present in the air. This applies to all canned foods except certain items that do not receive a sterilizing heat treatment and except frozen foods put up in cans. All of these, however, bear adequate warning on the label that the product should be kept refrigerated or frozen.

USE OF STETHOSCOPE BY PHYSICAL EDUCATORS

To the Editor:—*Is it out of line for the physical educator to use a stethoscope for training purposes to determine or evaluate his conditioning procedures by listening to the heart beat and pulse rate? Would it be improper for a physical educator to screen his regularly scheduled classes with a stethoscope and refer obvious weak or defective heart cases to a physician?* *M.D., Ohio.*

Answer.—Two basic assumptions apparently are involved in this inquiry. One is that the physical educator could be sufficiently well trained, through some procedure that is not indicated in the inquiry, to discriminate between normal and abnormal. The second is that, through following the practice proposed, it might be possible to improve detection of cardiac abnormalities. If the medical profession is to continue to subscribe to the fundamentals of medical training, neither of these assumptions can be accepted. Not only would it be unwise to have a medically untrained person making heart "examinations," but also such a practice could lead to much confusion. Serious heart conditions might easily be missed, or the physician would be called on constantly to clarify or interpret "symptoms" the lay examiner believed he had detected. The average physical educator probably would be the first to reject any such program, since he would recognize the inadequacies of his training so far as participation in a medical program would be concerned.

NASAL POLYPS

To the Editor:—*Please advise the present status of deep therapy and/or irradiation of nose to prevent recurrence of nasal polyps after surgery.* *M.D., Michigan.*

Answer.—Nasal polyps are most often the result of allergy, infection, or a combination of the two. Recurrence of nasal polyps after surgery will be prevented only when the underlying cause is completely understood, and this is best achieved by routine histological examination of the excised tissues. Moreover, the possibility of malignant disease is thereby excluded. Irradiation therapy does not actually prevent recurrence of nasal polyps but in occasional instances may delay their reappearance. It is not in general use, probably because of the increased recognition of the role of allergic factors in nasal and sinus disease and the growing reluctance of the medical profession to use irradiation for benign conditions. If used intranasally, the dosage and application must be carefully planned by an expert in order to avoid such unpleasant sequelae as dryness, crusting, and impaired olfaction.

HIGH LEUKOCYTE COUNT IN ASYMPTOMATIC MAN

To the Editor:—*Can a white blood cell count of 26,600 per cubic millimeter, with a normal differential count, be considered normal for a clinically asymptomatic patient? If not, what pathology would you suspect in the following case? A man, 57 years of age and in apparent good health, was seen Aug. 21, 1955, for the first time professionally. He came in simply to satisfy his family's wish for a physical check-up. His history was entirely without medical interest. Only once in his adult life had he visited a doctor professionally and that was to procure life insurance. The examination revealed moderate obesity, seriously worn down incisors (no cavities), and a diffuse erythema of the palms bilaterally. Only the blood displayed any peculiarity. The red blood cell count, hemoglobin level, and even the differential count were all found to be within normal limits.*

Robert G. Rothberg, M.D., Glenolden, Pa.

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—A white blood cell count of 26,600 per cubic millimeter is definitely abnormal, and such a leukocytosis demands further studies. The patient should have an x-ray of his mediastinum, tests for occult blood in his stools, and a bone marrow study. It should be recalled that a preleukemic state may reveal no other findings. That the differential count was normal should be verified by an expert hematologist.

Answer.—A white blood cell count of this magnitude is abnormal. There are physiological variations, but they seldom exceed 15% of the average normal. That many leukocytes imply the presence of (1) inflammation, (2) leukemia, or (3) leukemoid state. The differential blood cell count should suggest the nature of the condition. An increase in stab polymorphonuclear leukocytes indicates inflammation. Variable percentages of immature cells is a finding in leukemia. Leukemoid states are characterized by immaturity of myeloid cells and are associated with acute tuberculosis, syphilis, and polycythemia vera. With a normal clinical picture, it may be assumed that either the total white blood cell count or the differential count, or both, are inaccurate. There are numerous pitfalls in doing a white blood cell count. It requires skill to do a differential blood cell count. It would be well to repeat the blood work and seek the advice of someone skilled in hematology.